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## HEBERDEN ORATION, 1957\*

### GOUT

BY

KNUD BRØCHNER-MORTENSEN

*From Rigshospitalet, University Hospital, Medical Dept. A, Copenhagen*

Gout is one of the classics of medicine, first described more than 2,500 years ago; yet, although our knowledge about the disease is increasing, it still presents so many open questions that it remains a challenge to medical science.

Indeed, I hesitate to talk about gout in the country in which Sydenham (1683) gave his classic description of the clinical picture, Wollaston (1797) found uric acid in gouty deposits, Garrod (1848) demonstrated hyperuricaemia in patients with gout, and so many other important contributions to our present knowledge and understanding have been made.

Moreover, in a short lecture, it is not possible to cover more than a small section of the topic, but I will try to tell you a little about our experiences in Denmark in recent years.

**Incidence.**—This varies considerably from country to country, even within a small area such as Scandinavia.

Gout is very common in Denmark and southern Sweden, rare in northern Sweden and Norway, and apparently almost non-existent in Finland. Great Britain has long been considered the kingdom of gout and London its capital.

Some doctors in many countries feel that gout is disappearing, but more likely it is a forgotten disease—forgotten perhaps by the doctors, but certainly not by the patients.

In Denmark we have fairly good evidence that the incidence of gout was decreasing during the two world wars, but it has now again become fairly

common. It is very difficult to obtain exact information of the total number of cases, since only a few patients are hospitalized, but I would estimate that about 5-10 per cent. of male arthritis is gouty.

Everyone agrees that gout may be found—though rarely—in women, but most of the cases diagnosed in women are rather doubtful. I have seen tophaceous gout in three females, but I find that at least 95 per cent. and probably 98-99 per cent. occurs in male patients.

**Age at Onset.**—I have never observed an attack below the age of 20, but two of my patients claim that their first attack occurred at the age of 15.

In almost all cases gout first appears in the age group 25 to 60, but I have seen a first attack of primary gout in a man of 71 (Table I, overleaf).

**Weight and Drinking Habits.**—Table II (overleaf) shows that most of my patients are overweight (Brøchner-Mortensen, 1941).

Gout was formerly called the arthritis of the rich, but this is no longer so, at least not in Denmark, though certain professions (including bartenders, brewery-workers, and some salesmen) predominate among the patients.

It is difficult to obtain reliable information on drinking habits of patients, some being over modest in their statements, and some liking to boast a little.

Out of 93 of my patients thirteen said that they were teetotallers, 21 took one or two bottles of beer a day, 31 had five to ten bottles, and 17 more than ten bottles. A bottle of Danish beer contains 15-50 mg. of oxypurines. I should like to emphasize that this does not reflect the drinking habits of the average Dane.

\* The Heberden Oration was delivered before the Heberden Society at the Wellcome Foundation, London, on December 13, 1957.

TABLE I  
AGE AT FIRST ATTACK OF GOUT  
(PERCENTAGE DISTRIBUTION)

Age (yrs)	Scudamore (1866)	Williamson (1920)	Bröchner-Mortensen (1940)	Villa, Robecchi, and Ballabio, with de Séze, Ryckewaert, Levernieux, and Marteau (1958)
0-10	0	0	0	0
11-20	2	0	2	1
21-30	27	15	4	23
31-40	37	37	26	36
41-50	23	29	27	27
51-60	8	18	24	13
61-70	2	1	16	0
71-80	0	0	1	0

TABLE II  
WEIGHT OF PATIENTS WITH GOUT

Deviation from Standard Weight (per cent.)	Number of Patients
± 10	17
+ 11-20	17
+ 21-30	15
+ 31-40	13
+ 41-50	10
+ 51 and more	7

**Heredity.**—It has long been believed that gout was a hereditary disease. Various recent investigations show that hyperuricaemia without attacks is fairly common among the relatives of gouty patients, and the theory has been advanced that hyperuricaemia is the genetic factor in gout. Some authors conclude that hyperuricaemia is inherited as a dominant characteristic, but does not always lead to gouty manifestations.

In Denmark, Hauge and Harvald (1955) recently made a study of the relatives of 32 male probands with classic primary gout and a comparable control group. Table III shows that clinical signs of gout were found in sixteen of the relatives of the 32 probands—and none in the control series. Urinary calculi were found in twenty relatives and four controls.

Table IV shows that the mean value of serum uric acid was definitely higher in the siblings than in the controls even after deducting those in whom the diagnosis of gout was made.

The brothers as well as the sisters presented mean values 0.8 mg. per cent. above normal.

Our genetic experts, however, felt that there was insufficient evidence to support the assumption of a monomeric dominant or recessive inheritance,

TABLE III  
GOUT, URINARY CALCULI, CHOLELITHIASIS, AND DIABETES MELLITUS IN RELATIVES OF GOUTY PATIENTS AND A SERIES OF CONTROLS

Series	Propositi	Control
Total Number of Near Relatives (parents, siblings, children) ..	261	266
Gout		
Typical .. .. .	16	0
Atypical .. .. .	2	1
Urinary Calculi .. .. .	20	4
Cholelithiasis .. .. .	16	18
Diabetes Mellitus .. .. .	5	4

TABLE IV  
SERUM URIC ACID IN SIBLINGS OF PATIENTS WITH GOUT

Siblings	Brothers		Sisters	
	No.	Uric Acid (mg. per cent.)	No.	Uric Acid (mg. per cent.)
Total Material ..	47	6.1	57	5.4
Siblings without Arthritis ..	39	5.9	57	5.4
Normal Values ..		5.1		4.2

the serum urate level in each individual being probably influenced by a number of different genes.

**Uric Acid.**—Since the days of Wollaston and Garrod it has been thought that a disturbance of purine metabolism plays a decisive role in gout.

The important observations made in former days were hampered by unsatisfactory analytical methods. In the mid-19th century Garrod developed his thread method, which was ingenious but impracticable.



For many years Folin's phosphotungstic acid method and its numerous modifications was followed. The technique was easy but the method was neither specific nor quantitative, and the results obtained by the various modifications varied enormously. This fact was stressed again and again by Folin even in his last paper (Folin, 1934), but it was forgotten by most other workers using this so-called standardized method.

In 1935 I developed my ferricyanide method (Br chner-Mortensen, 1937). This was also very easy; it was quantitative but not quite specific, and consequently gave too high values in most cases.

The modern spectrophotometric enzymatic method (Table V) developed by Kalckar (1947), Praetorius (1947), and Praetorius and Poulsen (1953), and modified by others, is a little time-consuming and difficult except for well trained technicians, but it is apparently both specific and quantitative (Gj rup, Poulsen, and Praetorius, 1955). Research work of to-day ought to be carried out with methods based on this principle.

Hyperuricaemia is found in about 75 per cent. of early cases of gout (Br chner-Mortensen, 1940). It was previously believed that the level was higher before and during the acute attack than in the intervals, but I have not been able to confirm this. After 5 years' duration hyperuricaemia is found in most patients, but normal or only slightly elevated values may sometimes be found even in cases of severe tophaceous gout.

The determination of uric acid in serum for diagnostic purposes should never be performed in patients who have been given uricolytic agents within the last few days.

The total uric acid in the normal human body is about 1.1-2 g.; this was found by Gudzent (1928), and has been confirmed by modern experiments with labelled uric acid.

In gouty patients the total uric acid is increased to 5, 10, or 30 g. or even higher values.

The increased uric acid in patients with gout may

be caused by increased production, decreased destruction, decreased excretion.

(a) *Increased Production.*—Only a part, and probably a minor part, of the uric acid in the body is derived from preformed purine ingested, most being synthesized from non-purine precursors either directly or by way of nucleic acid.

The problem is whether the biosynthesis is higher in gout than in normal physiological conditions.

Studies by Benedict, Roche, Y , Bien, Gutman, and Stetten (1952) with ingestion of N<sup>15</sup> labelled glycine seem to support the theory that the biosynthesis of uric acid is greater in patients with primary gout than in normal individuals.

(b) *Decreased Destruction.*—The destruction of uric acid in man is still a matter of discussion. In man the presence of uricase has never been established.

Balance studies after the ingestion of uric acid or purine gave very conflicting results, but after the intravenous injection of labelled uric acid about 75 to 80 per cent. appeared as uric acid in the urine. This has been taken as evidence for the destruction of uric acid in man.

Wyngaarden and Stetten (1953) for instance, recovered 76 per cent. of the injected uric acid as uric acid in the urine, 16 to 18 per cent. of N<sup>15</sup> was found as urea, 1 per cent. as ammonia, and a small amount was found in the faeces.

I suspect that the N<sup>15</sup> recovered as urea and ammonia—or at least a part of it—derived from uric acid excreted in and broken down in the intestine.

So far we have no strong case for a metabolic destruction of uric acid in man and no evidence that patients with gout break down less uric acid than normal persons.

(c) *Decreased Excretion.*—The excretion of uric acid is a complicated process.

In many patients with gout, albuminuria and/or impairment of the renal function is found, and for many years it was thought that the hyperuricaemia

TABLE V  
NORMAL VALUES OF SERUM URIC ACID  
(SPECTROPHOTOMETRIC ENZYMATIC METHOD)

Sex	Number of Observations	Mean Value (mg. per cent.)	Normal Range (mg. per cent.)	Number of Observations within Normal Range (Mean $\pm 2 \times S$ )
Male	143	5.0	2.6-7.5	138 (97 per cent.)
Female	157	3.8	2.0-5.7	152 (97 per cent.)

When examined after 3 days' purine-free diet the values are about 1 mg. per cent. lower.

of gout was of renal origin. To-day it is the general opinion that renal insufficiency in gout is due to secondary damage or disease independent of the gout.

The normal renal excretion of uric acid on a purine-free diet is 300 to 400 mg. in 24 hrs, and the amount excreted in gouty patients without renal disease is about the same or even higher.

The mechanism for the renal excretion of uric acid has long been a matter of discussion. The prevailing concept is that uric acid is freely ultrafiltrable through the glomeruli and that about 90 per cent. is reabsorbed through the tubules, so that the resulting clearance is about 10 ml. per minute. Many years ago I demonstrated an augmentation limit at about 1 ml. per minute (Brøchner-Mortensen, 1937), and examinations should always be performed at a high diuresis. Uric acid clearance is about the same in gouty and non-gouty individuals on a purine-free diet. After the intravenous injection of uric acid or the ingestion of high-purine diet

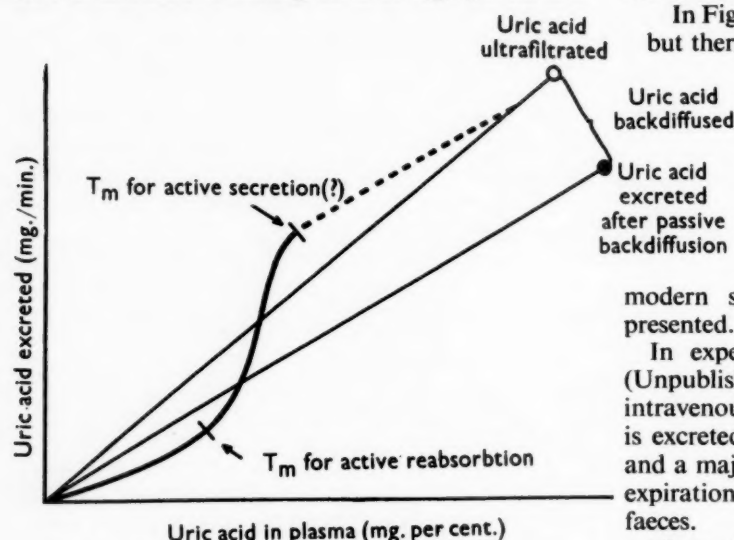


Fig. 1.—Theoretical mechanism of renal uric acid excretion.

the uric acid clearance will increase in most normal persons, but in most gouty patients the increase is absent or less pronounced (Brøchner-Mortensen, 1940).

Berliner, Hilton, Yü, and Kennedy (1950) found that the uric acid clearance increased in most persons with increasing levels of serum uric acid, and they suggested the presence of a  $T_m$  for uric acid with a maximal reabsorption capacity of about 15 mg. per minute. The level of  $T_m$  in gout has not been examined as far as I know.

Poulsen (1955) and Poulsen and Praetorius (1954) in Denmark have recently presented some very

interesting observations. In normal rabbits the ratio between uric acid clearance and creatinine clearance is 0.1 : 0.7 (average 0.4). This means that about one half of the uric acid is reabsorbed in the tubules. If, however, the serum uric acid level is increased by intravenous injection, the ratio increases to an average of 1.77. These findings suggest a secretion of uric acid.

If Probenecid is given to these animals, the ratio will drop to about 0.8 : 1.0, but not to the normal level of 0.40, possibly because Probenecid inhibits both secretion and reabsorption of uric acid.

A single observation made by Praetorius and Kirk (1950) suggests the secretion of uric acid in human tubules. In a man with a very low plasma uric acid they found the uric acid clearance to be higher than the filtration rate. The analysis was made by the spectrophotometric enzymatic technique.

The mechanism of uric acid excretion probably includes several processes; ultrafiltration, passive diffusion, secretion, and reabsorption.

In Fig. 1, I have tried to put these ideas together, but there are still several hypothetical points.

The kidneys are not the sole excretory organ for uric acid, for a little is excreted in the sweat, and some in the gastro-intestinal tract.

Lucke (1932) estimated that extra-renal excretion amounted to some 40 to 70 mg. per 24 hours, but until recently no investigations with isotopes and

modern specific analytical technique have been presented.

In experiments with  $2\text{-C}^{14}$  uric acid Sørensen (Unpublished work) has estimated that, after the intravenous injection of uric acid, up to one-third is excreted in the intestines; it is rapidly destroyed and a major part of  $\text{C}^{14}$  may be recovered from the expiration as  $\text{CO}_2$  and a minor part from the faeces.

There is thus very suggestive evidence for an increased production of uric acid in gout, but no definite evidence for metabolic destruction of uric acid in man, and consequently none for decreased destruction in gouty men.

The old idea of a decreased excretion of uric acid in gout is not supported by recent investigations, but our knowledge is still very incomplete in many respects, as regards renal and extrarenal excretion, the latter being probably greater than previously thought.

We know that there is an accumulation of uric acid in patients with gout, but we have no proof that this is responsible for every sign and symptom of the disease. The deposition of uric acid explains

the tophi and some of the deformities, but we still do not know the cause of acute attacks.

It is probably too simple an explanation that the acute attack is a tissue reaction to the irritating crystals.

Some believe that the depositions are secondary to the arthritis, but I have found, during a first attack, large urate deposits in a joint which had been opened by a surgeon who thought it was due to suppurative arthritis.

### Treatment

The physician has to face two main therapeutic problems: the treatment of the acute arthritis, and the prevention of new attacks and other signs and symptoms.

#### Colchicine

In the treatment of the acute attack colchicine was the ruling remedy for 1,500 years. It was known by the Egyptians, but apparently Psychristes, in the 6th cent. A.D., was the first to recommend it as a specific agent against gout. Its therapeutic mechanism has never been elucidated.

Colchicine may be given in many ways. I generally gave 0.5 mg. every hour for 8 to 10 hrs for 2 or sometimes 3 days. The individual dose can generally be adjusted by trial and error.

It is active in most cases, even if diarrhoea does not occur, and is well tolerated by most patients, though some were troubled with rather severe diarrhoea and nausea, and many years ago I saw an aged feeble patient die from heart failure during severe diarrhoea caused by colchicine. The intravenous administration of colchicine may be of great help but gastro-intestinal disturbances sometimes ensue.

Various related compounds have been tried, especially Colcemid, but their advantage over colchicine seems to be small.

#### Phenylbutazone

Since the appearance on the market of phenylbutazone this has been my treatment of choice for acute attacks, but on account of the often severe side-effects I hesitate to give it over a long period.

The administration should be individualized, but very often I give 800 mg. on the first day, 400 or 600 the next day, and sometimes 200 for another 2 or 3 days. Its action is generally prompt, and most patients who have previously had colchicine prefer phenylbutazone.

The drug is uricosuric, but the effect during the acute attacks is too quick to be explained in this way, and there must be a more direct action antiphlogistic on the joints.

Newer compounds, such as G25671 and others, have been produced, but their value is probably not much different.

### Other Measures

Cinchophen and similar compounds are no longer of interest, and their toxicity is such that we relinquish them without regret.

Treatment with adrenocortical steroids and especially corticotrophin may be of value in a few cases resistant to other forms of treatment. Their action may be very prompt, but a new attack may follow cessation of treatment. This recurrence can sometimes be prevented by giving colchicine or phenylbutazone prophylactically.

During the acute attack the affected joint should be kept at rest, but as far as possible or as soon as possible the patient should be allowed to get up.

Inactivity of the joint over longer periods should be avoided.

When phenylbutazone is given it is generally not necessary to give other analgesics, and I never prescribe hot or cold compresses.

When the acute attack is over the physician will face the much more difficult problem of preventing new attacks and other signs and symptoms.

### Diet

So far, it is not possible to influence the metabolic disorder, but an effort must be made to diminish the ingestion of purines and increase the excretion of uric acid.

It has been a matter of discussion whether low-purine diet is of any value, but we know for certain that a full diet will overload the organism with some 100-200 mg. of uric acid per 24 hrs and often more; consequently I find it reasonable to diminish the ingestion of purines as far as possible without harming the patient physically and mentally.

I prescribe a diet low in purine, poor in fat and calories, and slightly limited in meat, fish, and fowl. The patient is urged to eat boiled meat and let his wife have the soup.

In most cases the patient's weight should be reduced, and his drinking habits corrected. Beer is probably most harmful. Distilled spirits on the whole are well tolerated, but some patients claim that certain alcoholic drinks provoke acute attacks, and this apparently differs from individual to individual.



### Diuresis

Patients should be urged to maintain a high rate of diuresis since the renal excretion is greatest when the diuresis is kept above the augmentation limit, about 1 ml. per minute.

### Uricosuric Agents

For many years it has been known that a number of substances, including salicylates, cinchophen, and mercurial diuretics, will increase the renal excretion of uric acid, and during the last few years interest has centred in Probenecid.

Dioscorides (cited by Gross and Greenberg, 1948) wrote in the 1st cent. A.D., *In re materia medica*, that willow bark should be given to patients with gout, and Byasson (1877) found that salicylates had a uricosuric effect.

The mechanism of this effect is apparently fairly complicated. A transitory increase in serum uric acid was found by Crone and Lassen (1955c) when small doses of 1 to 3 g. per day were given (Fig. 2).

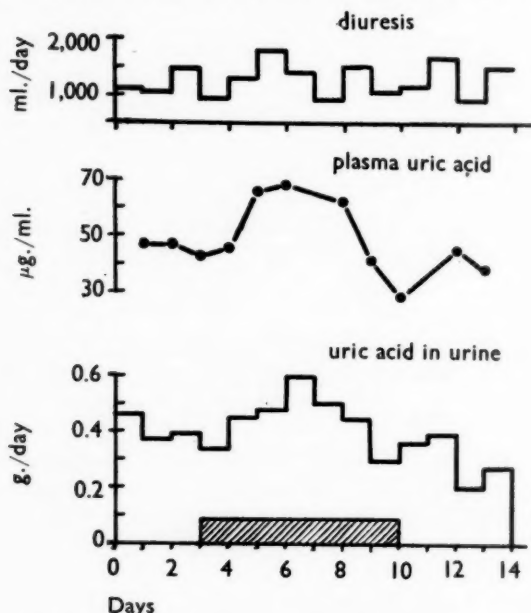


Fig. 2.—Uric acid in blood and urine after administration of 3 g. acetylsalicylic acid per 24 hrs.

In four out of seven experiments the excretion was unchanged, in three an increase was observed, and no decrease was seen.

After higher doses, for instance 6 g. per day (Fig. 3), there was no elevation of serum uric acid and in all cases the renal excretion was markedly increased.

The action on the kidney (Fig. 4, opposite) apparently involves an inhibition of tubular reabsorption

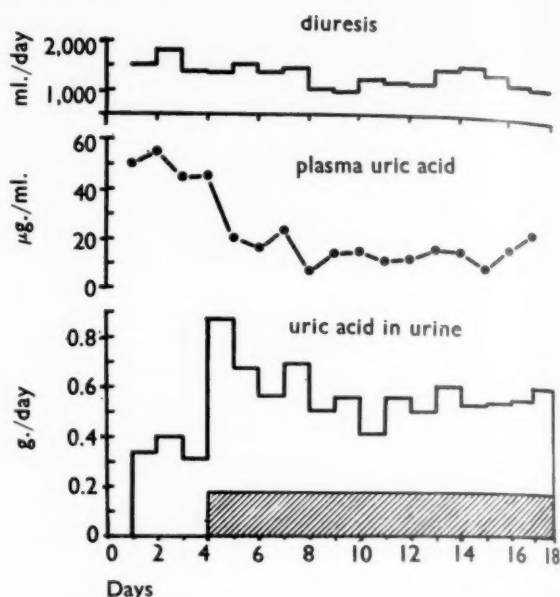


Fig. 3.—Uric acid in blood and urine after administration of 6 g. salicylic acid per 24 hrs.

(Crone and Lassen, 1955d). In order to obtain a marked uricosuric effect over prolonged periods, it is generally necessary to give rather large doses of salicylates, and at least on our side of the North Sea this has generally resulted in rather pronounced side-effects, and we generally prefer to give Probenecid.

Probenecid acts very quickly. After 1 hr the excretion is augmented, the maximum is reached after 2 to 5 hrs and the effect will generally last for 9 hrs (Crone and Lassen, 1955a). It should therefore be given in at least three divided doses in 24 hrs (Fig. 5, opposite).

The uricosuric effect (Fig. 6, opposite) is apparently due to inhibition of tubular reabsorption (Crone and Lassen, 1955b).

When salicylate is added to Probenecid (Fig. 7, overleaf) the excretion decreases rapidly (Lassen, unpublished work).

The action of Probenecid can be maintained over a very long period, probably indefinitely. We have closely followed about fifteen patients for 2 years or more.

We generally start with 0.5 g. per day, slowly increasing the dose to about 1.5 g. according to the serum level.

In some patients we have seen a definite reduction of tophi, and especially the drying up of fistulae from tophi.

Side-effects on the whole have been moderate; in two patients we had to discontinue the treatment

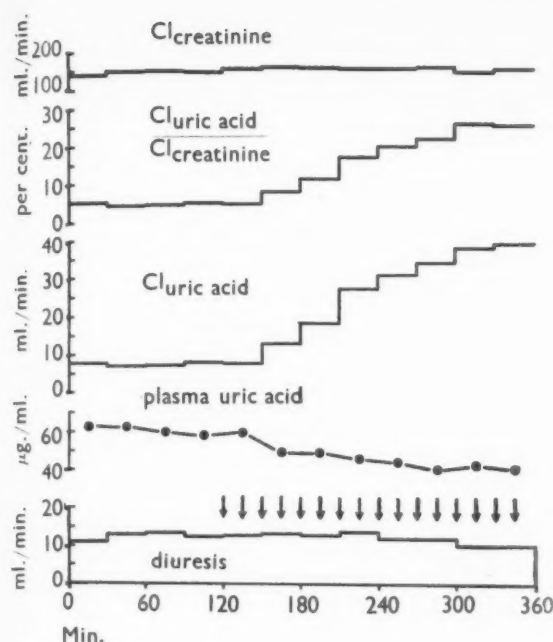


Fig. 4.—Effect of salicylic acid on creatinine and uric acid clearance. Each arrow indicates the administration of 250 mg. salicylic acid.

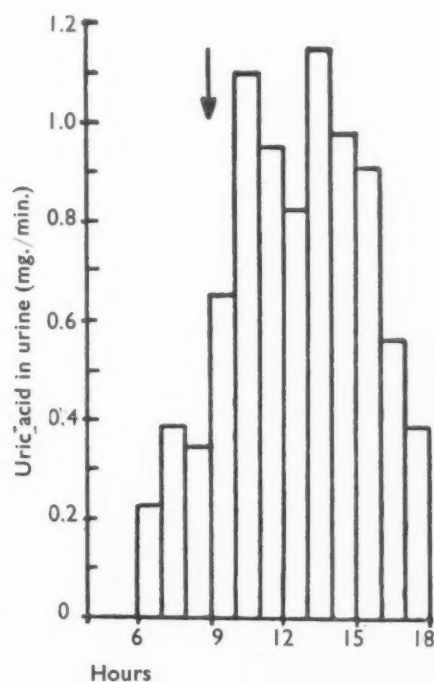


Fig. 5.—Uric acid excretion before and after administration of 0.2 g. Probenecid. Arrow indicates time of administration.

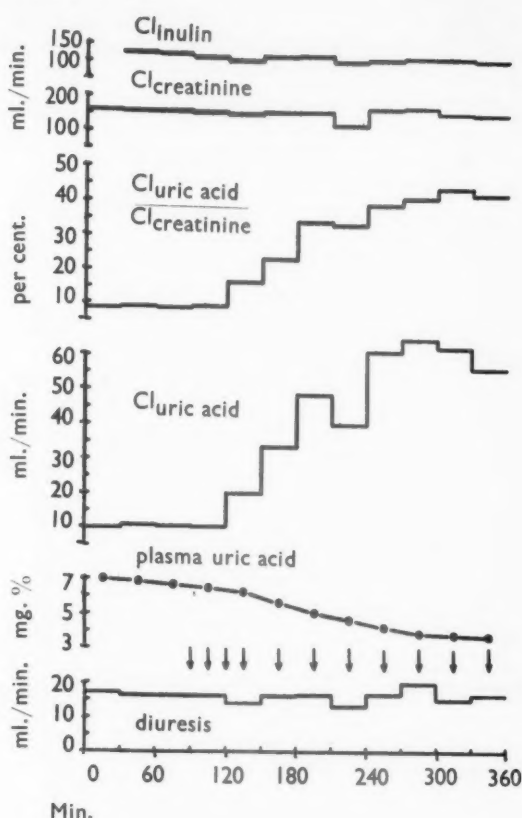


Fig. 6.—Effect of Probenecid on creatinine and uric acid clearance. Each arrow indicates the administration of 0.5 g. Probenecid.

on account of nausea, but we saw no exanthema and no renal calculi. We have kept the urine alkaline, and urged the patients to maintain a large diuresis.

In one patient we gave Probenecid in spite of the presence of large calculi.

The patient was a 70-year-old postmaster who had polycythaemia and secondary gout with many attacks and big fistulizing tophi. One kidney was completely blocked with calculi, and there were large stones in the other, so that the kidney function was about 20 per cent. of normal. The blood urea was about 100 mg. per cent., and the serum uric acid level 17 mg. per cent. On 0.5 to 1 g. Probenecid the serum uric acid dropped to about 10 mg. per cent., the uric acid excretion was about 1 g. per day, the tophi diminished, the fistulae dried up, and the attack rate was diminished. After about 2 years he died from a cerebral thrombosis.

### Conclusion

Gout has troubled man for thousands of years, but to-day it is possible by well-planned and well-

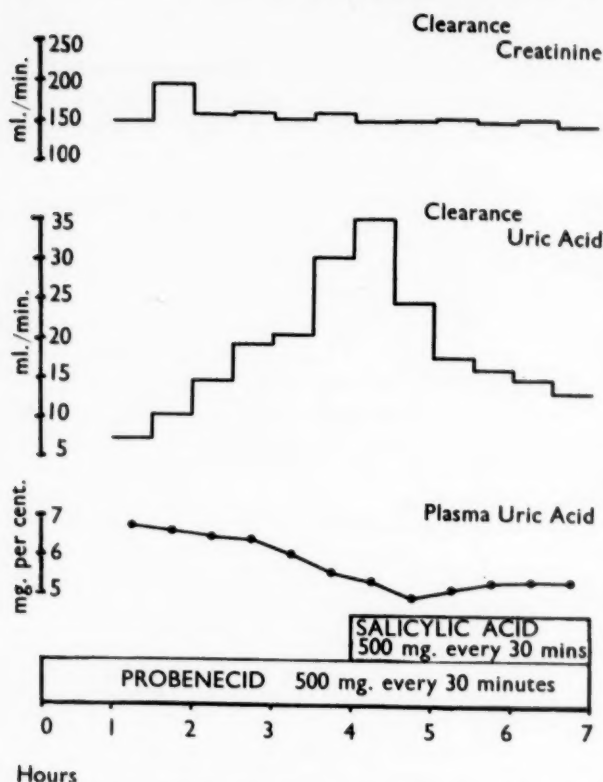


Fig. 7.—Effect of Probenecid and salicylic acid on creatinine and uric acid clearance

conducted treatment to keep the disease under control in most cases.

From a theoretical point of view the situation is less satisfactory, since most of the problems concerning the aetiology and pathogenesis are still unsolved and gout still presents a challenge to medical science.

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PHYSIOPATHOLOGY, CLINICAL MANIFESTATIONS,  
AND TREATMENT OF GOUT\*  
PART 1. PHYSIOPATHOLOGY AND PATHOGENESIS

BY

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This report deals with our experience with about 100 patients investigated by the laboratory tests and methods set out in Table I.

Any definition of gout must take into account the two fundamental aspects of the disease: the metabolic disturbance on the one hand, and the anatomical and clinical picture on the other.

The first, which characterizes the so-called "gouty diathesis", is seen in a 20- to 30-fold increase in the uric acid pool, as demonstrated by radio-isotope technique, and is accompanied in most cases by a rise in the blood uric acid level (Benedict, Forsham, and Stetten, 1949; Benedict, Forsham, Roche, Soloway, and Stetten, 1950; Bishop, Garner, and Talbott, 1951; Bishop, Rand, and Talbott, 1955; Talbott, 1957). The second aspect is represented by the suggestion of an allergic component in the clinico-pathological picture.

A metabolite may accumulate in the body because of inadequate breakdown, reduced excretion, or excessive formation. The absence of uricase in man has been fairly well established, and the possibility of uric acid oxidation by other enzymes, such as cytochrome oxidase or verdoperoxidase, has been considered (Agner, 1943; Margules and Griffith, 1950). We have already demonstrated (Villa, Polli, and Bussi, 1953) the uricolytic properties of leucocyte extracts, and we have found, after further investigation, that this action is not of the uricase type, and resides preferentially in cells of the myeloid series (Ratti and Cirla, 1957).

The importance of the kidney in regulating the uric acid pool is demonstrated by the low rate of urate clearance which, according to our findings (Sala, Ballabio, and Amira, 1955; Sala, Ballabio,

TABLE I  
METHODS USED IN LABORATORY TESTS

Investigation	Method	
	Authors	Date
Plasma uric acid	Brown	1945
Urinary uric acid	Benedict and Franke	1922
Urinary uric acid (C <sup>14</sup> )	Benedict, Forsham, and Stetten	1949
Plasma and urinary uric acid	Praetorius and Poulsen (Uricase Leo)	1953
Uric acid electrophoresis	Salteri and Cirla	1956
Sodium thiosulphate	Brun	1950
P.A.H.	Smith, Finkelstein, Alimnosa, Crawford, and Graber	1945
Plasma and urinary endogenous creatinine	Bonsnes and Taussky	1945
Urinary 17-ketosteroids	Callow, Callow, and Emmens	1938
Plasma 17-ketosteroids	Ceresa and Cravetto	1957
Urinary 17-hydroxycorticosteroids	Silber and Porter	1954
Plasma 17-hydroxycorticosteroids	Ceresa and Cravetto	1957
17-ketosteroid chromatography	Dingenmanse, Huis in't Veld, and Hartogh-Katz	1952
Urinary purine	Williams	1950
Purine chromatography	Horrigan	1954
	Weismann, Bromberg, and Gutman	1954
	Lucchelli and Crosti	1956
Lipoprotein electrophoresis	Fasoli and Salteri	1955
Lipoprotein ultracentrifugation	Green, Lewis, and Page	1951
Cholesterolaemia	Bloor	1916

\* Presented at the IX International Congress of Rheumatic Diseases at Toronto, Canada, in June, 1957.



Amira, Ratti, and Cirila, 1956) and those of other authors (Brøchner-Mortensen, 1939; Mugler, Pernet, Pernet, and Friedrich, 1955), amounts to between 8 and 10 ml./min. in normal subjects. Excretory insufficiency is regarded as a result of diminished glomerular filtration caused by physico-chemical changes in the blood uric acid. The possibility that plasma uric acid may be present in a non-dialysable form, *i.e.* bound to plasma proteins, has been investigated by several authors, including Wolfson, Levine, Guterman, Hunt, Cohn, and Rosenberg (1948) and Adlersberg, Grishman, and Sobotka (1942). According to the latter group of workers, in certain pathological conditions, especially in gout, the bound uric acid may reach 65 per cent. On the other hand, Yü and Gutman (1953, 1955) state that the plasma urate is completely filtered by the glomerulus, while Bordley and Richards (1933) have demonstrated that the concentration of uric acid in the tubular urine of the frog was the same as that in the blood.

We have investigated the electrophoretic behaviour of uric acid in 160 samples from 42 subjects, and we have reached the following conclusions (Fig. 1):

- (1) Under specific experimental conditions the electrophoretic migration of serum uric acid can be readily differentiated from that of serum protein by its characteristic band before the peak of albumin. The result is the same when uric acid is added to serum *in vitro*.
- (2) Elution of this band leads to the recovery of 85 to 100 per cent. of the serum uric acid, but only insignificant amounts can be recovered from other sections of the paper. These findings suggest that uric acid lacks the power to bind protein, and that ultrafiltration is complete;

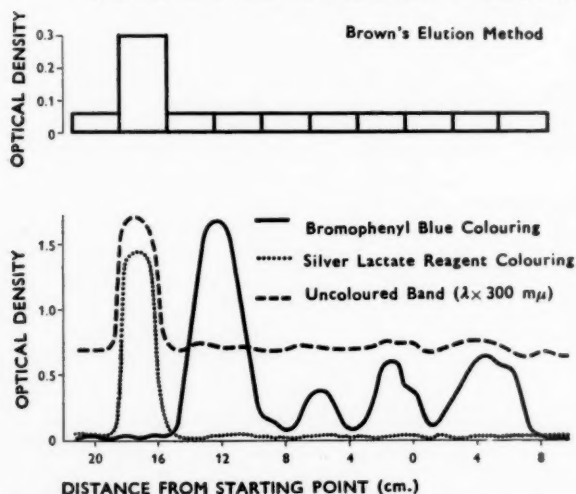


Fig. 1.—Electrophoretic behaviour of uric acid in 160 samples from 42 subjects.

they do not support the idea that insufficient glomerular filtration may be due to physico-chemical peculiarities of the plasma uric acid.

The following results were obtained in a study of the renal excretion of uric acid in 56 subjects (Fig. 2, opposite):

- (1) In the normal subject, with an average plasma uric acid value of 4.4 mg. per cent. and a urinary urate excretion of 0.405 mg./min., the urate clearance was calculated to be 9.2 ml./min. This signifies that, with a glomerular filtration of 111 ml./min., 91.7 per cent. of the filtered urate was reabsorbed.
- (2) In gouty subjects, with corresponding values of 8.30 mg. per cent. and 0.393 mg./min., the urate clearance was 4.7 ml./min. This signifies that, with a glomerular filtration rate of 112 ml./min., 95.8 per cent. of the filtered urate was reabsorbed. Thus in 74 per cent. of our gouty subjects there was an increase in the tubular reabsorption of urate.
- (3) An adaptation of the tubule cell to an increased excretion of uric acid is noted in other pathological conditions, and our studies in leukaemic subjects have revealed that the amount reabsorbed by the tubules may be as low as 86 per cent. The urinary urate excretion increased and the urate clearance rose to 14.2 ml./min.; in single cases the urate clearance value rose to 34 ml./min.

A reduction in the amount filtered by the glomerulus intensifies the excretory insufficiency, but in the gouty subject with renal insufficiency the ratio of filtered urate to excreted urate reveals the same type of tubular dysfunction as is seen in gouty patients without renal insufficiency (Ballabio and Ortenzi, 1957). These results are significant within the 5 per cent. limit ( $P < 0.01$ ) and do not agree with those of certain other authors (Berglund and Frisk, 1935; Coombs, Pecora, Thorogood, Consolazio, and Talbott, 1940; Brøchner-Mortensen, 1939), but the findings of Mugler and others (1955) in a large series of cases are in essential agreement with ours.

The significance of the tubule in regulating the miscible urate pool has been emphasized by the recently discovered uricosuric action of Benemid (Probenecid), which inhibits tubular reabsorption of urate (Bishop and others, 1951; Bishop and Talbott, 1953; Friedman, 1948; Sirotta and Yü, 1952; Sirotta, Yü, and Gutman, 1952; Ballabio, Ratti, and Amira, 1954; Talbott, 1957).

Paton, Brodie, Yü, Burns, Chenkin, Steele, and Gutman (1955) and Ballabio and Ortenzi (1957) suggest that the uricosuric action of G 25671 operates by a similar mechanism. We have also confirmed the claim of Gleason, Street, and Kahn (1956) that Pyrazinamide is capable of augmenting

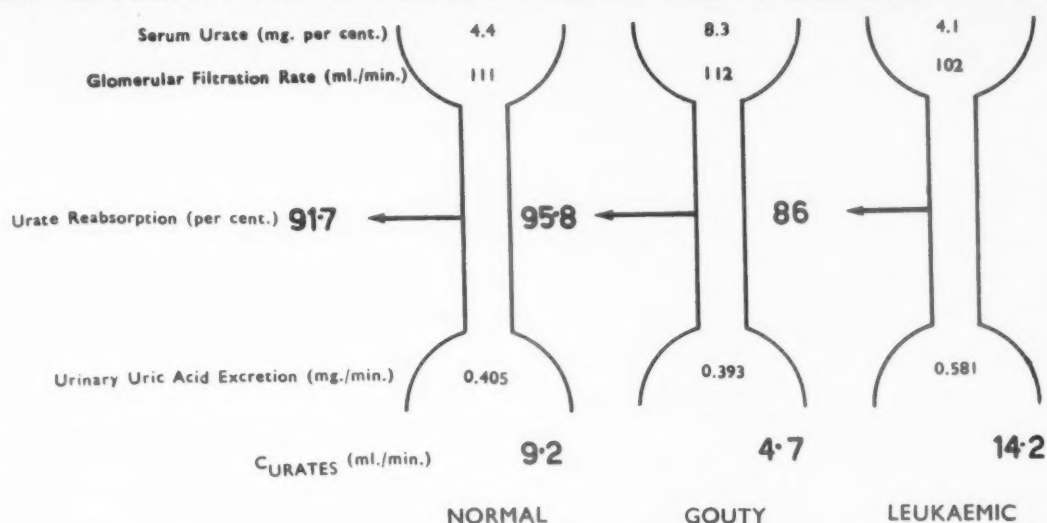


Fig. 2.—Renal excretion of urate in 56 normal, gouty, and leukaemic subjects.

plasma urate levels and lowering urinary urate excretion, by studying its effects in sixteen normal and gouty subjects. Fig. 3 shows the increase in plasma urate levels produced by Pyrazinamide. In a normal subject, the urate levels rose from 4 to 7.6 mg. per cent., and in a gouty patient they rose from 9.8 to 12.2 mg. per cent. Urinary urate excretion and urate clearance both decreased simultaneously.

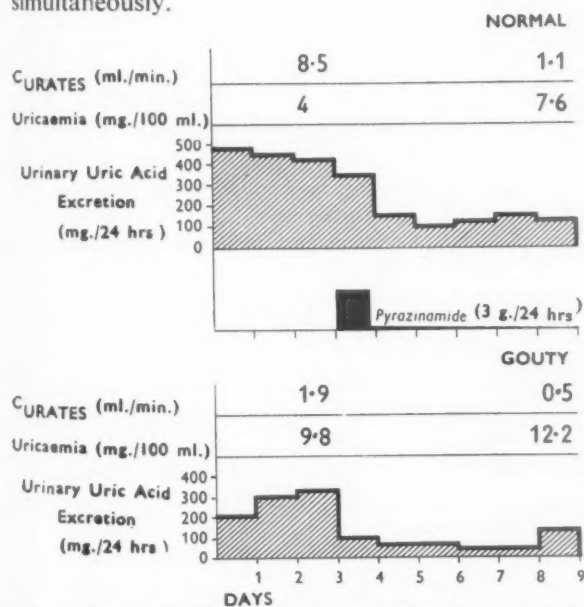


Fig. 3.—Effect of Pyrazinamide on uric acid excretion in a normal subject and a gouty patient.

Studies of the endogenous creatinine, thiosulphate, and *p*-aminohippurate clearances, as well as the

ratio of urate excreted to urate filtered, has shown that the renal tubule cell is the operational centre, Pyrazinamide having an effect opposite to that of Benemid.

Uric acid synthesis in the organism has been studied in recent years by the injection of labelled radioactive substances (isotopes), and it has been learned that uric acid is synthesized from relatively simple units, such as carbon dioxide, "formate", and  $\text{NH}_3$  as obtained from the nitrogen pool, particularly glycine, glutamine, and aspartic acid (Buchanan, Sonne, and Delluva, 1948; Greenberg, 1951; Shemin and Rittenberg, 1947; Stetten and Fox, 1945). The first link in the biosynthetic chain is formed by a condensation of glutamine with 5-phospho-ribosyl-pyrophosphate, giving rise to a phospho-ribosyl-amine. Further synthesis results in a 4(5)-amino-5(4)-imidazol-carboxamide ribotide which is converted to inosinic acid (hypoxanthine ribotide). At this point purine metabolism may progress either to the classical synthesis of purine bases up to nucleic acids, or directly to hypoxanthine and uric acid.

Investigations with  $\text{N}^{15}$ -glycine (Benedict, Roche, Yü, Bien, Gutman, and Stetten, 1952; Bishop, Rand, and Talbott, 1955; Muller and Bauer, 1953), with  $4\text{-C}^{13}$ -4-amino-5-imidazolcarboxamide (Seegmiller, Laster, and Stetten, 1955; Seegmiller, 1957), and with  $\text{C}^{14}$ -formate (Spilman, 1953), have demonstrated an increased biosynthesis of uric acid in certain gouty subjects, particularly in the presence of an increased urinary excretion of urate. We have also followed the fate of  $\text{C}^{14}$ -formate (100 microcuries) in a normal subject and in a patient with

chronic gout exhibiting typical tophi and low uraturia (Fig. 4). In this gouty patient there was no evidence of an increased incorporation of the isotope into the uric acid excreted in the urine. These data confirm that the increased production of uric acid is not a constant finding in the gouty subject (Benedict and others, 1953); Muller and Bauer, 1954), but recent work by Wyngaarden (1955, 1957) and Wyngaarden and Blair (1955) with  $C^{14}$ -glycine has shown that this increased biosynthesis is present in practically all gouty individuals.

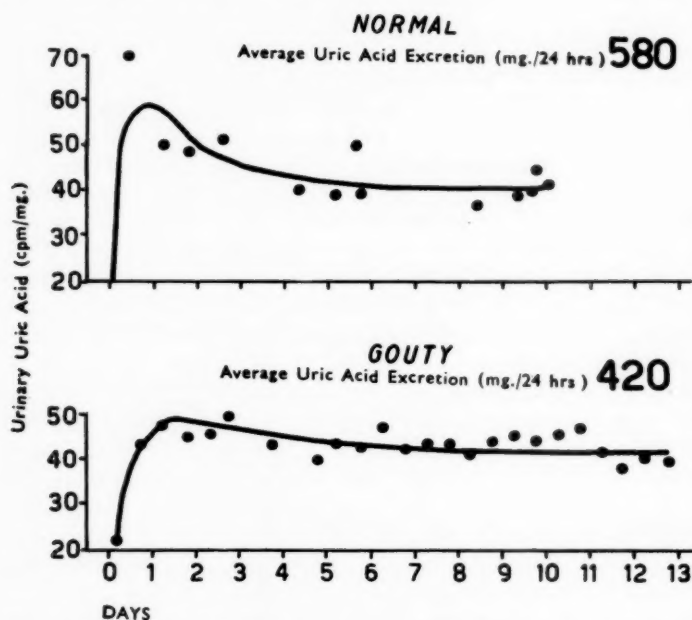


Fig. 4.—Incorporation of  $C^{14}$  formate into urinary uric acid in a normal subject and a patient with chronic gout.

According to Wolfson and Levine (1948), Wolfson and others (1948), and Wolfson, Guterman, Levine, Cohn, Hunt and Rosenberg (1956), the pathogenesis of gout may be attributed to a specific endocrine alteration, consisting in a diminished urinary excretion of 17-ketosteroids. This decrease may arise from the production of abnormal androgens in the adrenal cortex, a manifestation of adrenocortical insufficiency, which in turn is the result of decreased ACTH production. A certain degree of adrenocortical insufficiency may frequently be present in gouty subjects, and the metabolic changes which precede and follow an acute attack (described by Talbott (1957) as the "cycle of gout"), the frequency with which an acute attack follows a state of stress, and the rapid relapse when ACTH therapy is discontinued, all support the idea of such a deficiency. The urinary excretion of 17-ketosteroids was followed in 73 gouty subjects (Table II).

TABLE II  
URINARY EXCRETION OF 17-KETOSTEROIDS  
IN 73 GOUTY SUBJECTS

17-ketosteroids (mg./24 hrs)	Cases		Average (mg./24 hrs)
	No.	Per cent.	
< 6	10	13.7	4.5
6 to 11	42	57.6	8.2
> 11	21	28.7	13.2

A reduction was noted in 71 per cent. of these patients and this reduction was less than 6 mg./24 hrs in only 13 per cent. Chromatographic analysis in four cases showed that the diminution involved either the adrenocortical or the gonadal androgens. Blood and urinary 17-hydroxycorticosteroids and blood 17-ketosteroids were not far from normal values. It therefore appears that, considering the age and sex of the individuals involved, the abnormal gonadal and adrenocortical secretions do not play an important role in the pathogenesis of gout.

The difficulty of confining the problem of gout to that of uric acid metabolism has created interest in the possibility that certain quantitative or qualitative abnormalities in the degradation of nucleoproteins may be responsible for the disorder. According to our findings in thirteen gouty subjects, the quantitative purinuria (Fig. 5, opposite), in terms of the guanine, hypoxanthine, and xanthine excreted, is equal to that in normal subjects, in contrast with acute leukaemia in which both urate and purine excretion is considerably increased (Ratti and Cirila, 1957). Recent column and paper chromatographic studies (Weisman, Bromberg, and Gutman, 1957; Horrigan, 1954) have revealed in normal subjects an entire series of purine bases in addition to uric acid: xanthine, hypoxanthine, adenine, 7-methylguanine, guanine, 1-methylguanine, 1-methylxanthine, 7-methylxanthine, paraguine, and other substances not yet identified chemically.

Our work has been based on the method of Horrigan (1954), and we have carried the study of eluates a stage further by additional chromatography, using the technique of Cohn (1949), and on paper (Fig. 6, opposite). We are still identifying further purine bodies, but, on the basis of analyses in five gouty subjects, we have found no significant

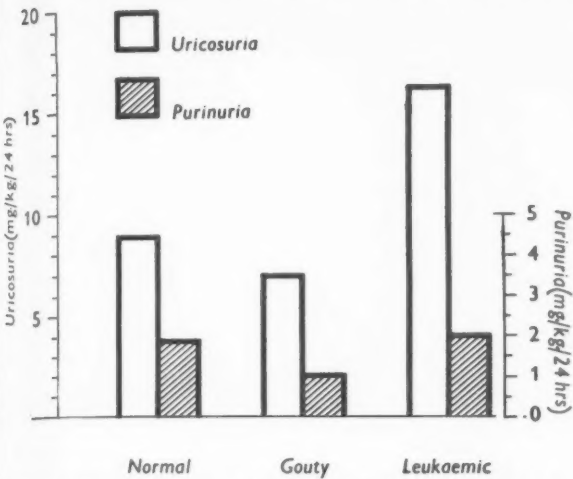


Fig. 5.—Excretion of uric acid and purines in normal, gouty, and leukaemic subjects.

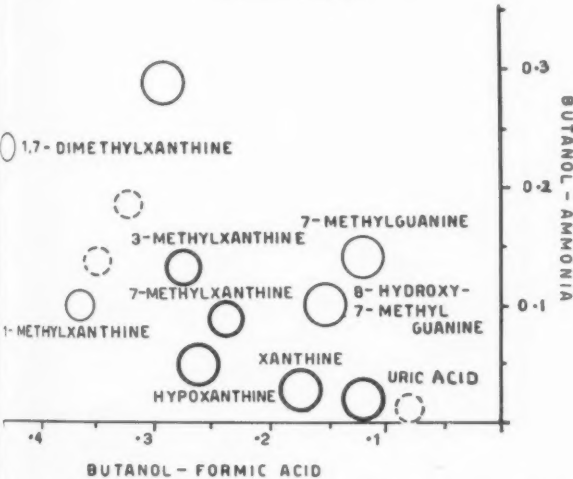


Fig. 6.—Chromatography of urinary purines in a gouty subject. Thickness of circles indicates intensity of colour.

difference from the normal.

The frequent association of obesity and arterio-sclerosis with the clinical picture of gout has suggested to several authors the possibility of a derangement in lipid metabolism (Greppi, 1956; Isemein, Ciaudo, Hawthorn, Lègre, Courtieux, and Ramis, 1956). The distribution of serum lipo-

proteins was studied in eighteen gouty subjects by paper electrophoresis and in nine cases by ultracentrifugation. The results (Tables III and IV) are as follows:

- (1) Paper electrophoresis showed a reduction in the  $\alpha_1$ -lipoproteins in gouty subjects, and a higher proportion of  $\beta$ -lipoproteins. This change is statistically significant ( $P < 0.001$ ).
- (2) Studies with the ultracentrifuge showed a statistically significant ( $P < 0.05$ ) reduction in the  $\alpha_1$  (Class  $S_{1.21}:0.15$ ) fraction. The most marked change ( $P < 0.001$ ) was an increase in the  $\beta$ -fraction of lowest density (Class  $S_{1.21}:60-400$ ).
- (3) The alteration in the lipoprotein equilibrium which is frequently present in gouty subjects suggests that the ability to elaborate large lipoprotein molecules is reduced.
- (4) The average cholesterol value in 62 gouty subjects was 218.8 mg. per cent.
- (5) These changes were not sufficiently characteristic to permit differentiation from the more general "atherogenic" type.

The possibility that gout has an allergic basis is suggested by several factors:

- (1) The difficulty of interpreting the disease on the basis of a single metabolic alteration.
- (2) The presence of an acute attack of gout with normal blood uric acid levels or alternatively the presence of primary or secondary hyperuricaemia during an entire life-time without gouty manifestations.
- (3) The analogous appearance of acute gout and anaphylaxis.
- (4) Hypersensitivity and vascular phenomena suggesting increased permeability in gouty subjects.
- (5) The dissociation between therapeutic results and metabolic alterations.

TABLE III  
LIPOPROTEIN PATTERN  
ELECTROPHORESIS

Subjects	No. of Cases	Alb.- $\alpha_1$		$\alpha_1$ - $\beta_1$		$\beta_2$	
		Mean	S.D.	Mean	S.D.	Mean	S.D.
Normal .. ..	16	29.5	9.1	56.1	8.3	14.4	4.4
Gouty Patients ..	18	12.5	5.3	73.4	6.0	14.1	4.4

TABLE IV  
LIPOPROTEIN PATTERN  
ULTRACENTRIFUGATION

Subjects	No. of Cases	- $S_{1.21}0.15$		15-25		25-33		33-60		60-400	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Normal .. ..	9	31.3	7.3	4.1	1.3	39.5	8.0	14.9	7.6	10.2	5.8
Gouty Patients ..	9	23.7	6.9	3.9	1.7	35.9	6.4	16.0	6.0	20.5	6.0



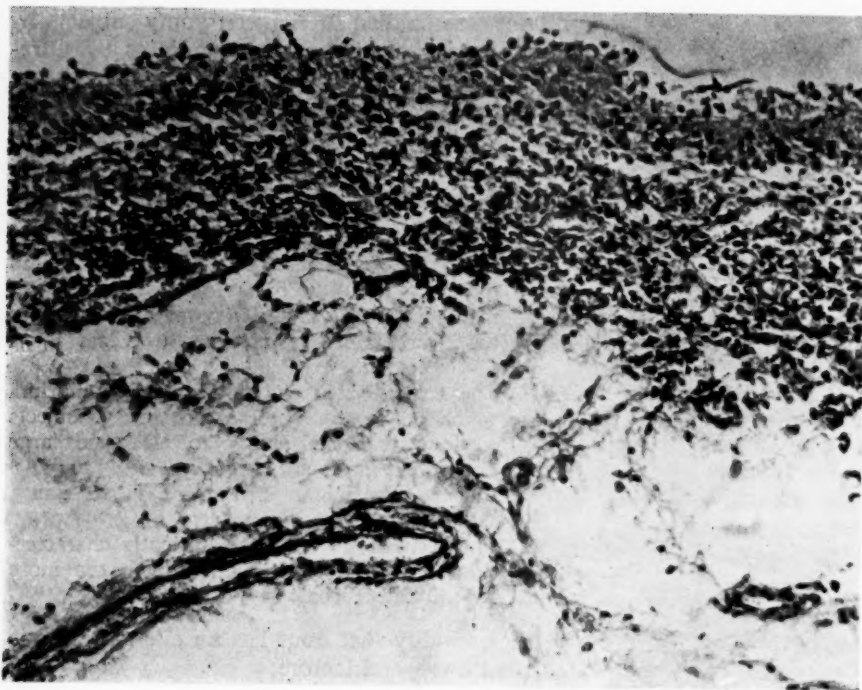


Fig. 7.—Biopsy of synovial membrane from a patient suffering from a first attack of gout, showing acute and mainly exudative inflammation without urate deposits.

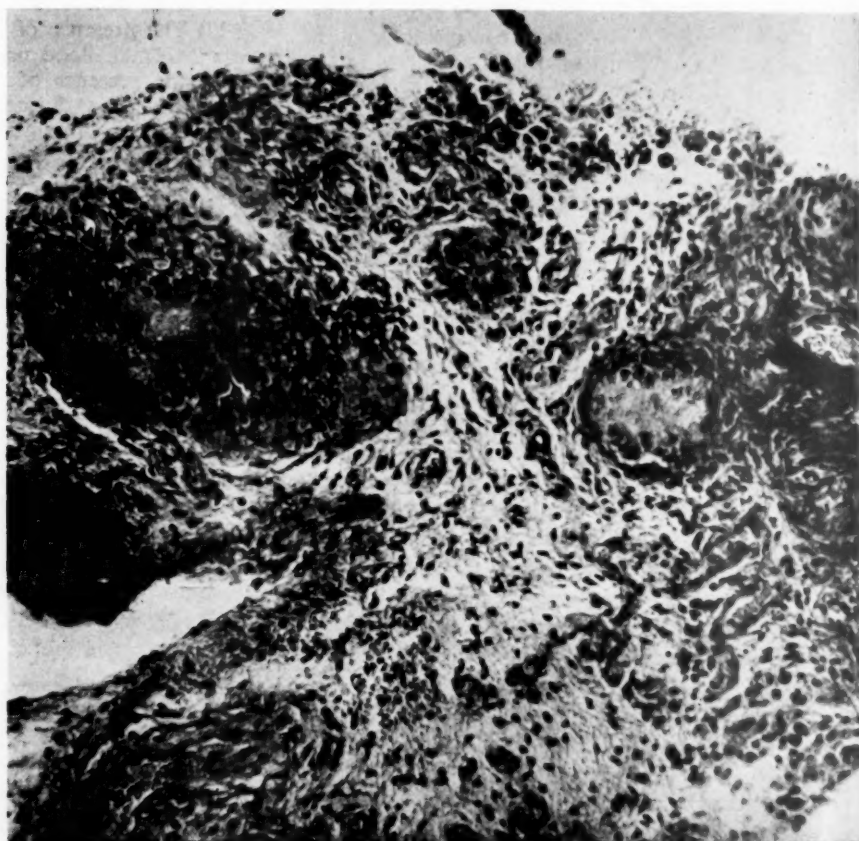


Fig. 8.—Biopsy of synovial membrane from a patient with chronic relapsing gout, showing granulomatous inflammation with giant cells related to advanced urate deposits.

The characteristic histological changes resulting from gout were studied in biopsies of affected tissue. Fig. 7 shows biopsy material from a patient suffering a first acute attack of gout, whereas previous studies have only shown tissue removed from chronic cases. There is acute inflammation in the absence of urate crystals, and this is in marked contrast to Fig. 8, taken from a patient with chronic gout, which shows urate deposits accompanied by a typical foreign-body reaction with giant cells. Sokoloff (1957) has recently reported the presence of uric acid crystals during an early attack of acute gout, which, however, was not the first one.

Association between clinical phenomena and metabolic alterations may be noted according to the type of therapy used. This is particularly apparent with colchicine, the therapeutic action of which appears to us to be independent of any direct metabolic interference. The contrary is observed with Benemid, which has no therapeutic value in the acute episode but, because of its uricosuric action, is the drug of choice for the treatment of chronic gout. Administration of Pyrazinamide does not induce acute gout, even in gouty subjects, whose plasma urate values may reach extraordinarily high values (personal observations). According to other authors, rheumatic complaints develop only after administration of this substance for several months.

#### SUMMARY OF PART ONE

The pathogenesis of gout is far from being solved, but the most recent findings and our own present

results make it possible to draw the following conclusions:

- (1) In gout there is an increase in the miscible urate pool.
- (2) An increased tubular reabsorption of uric acid and a diminished urate clearance are present in gouty subjects, even when the amount of urate excreted does not significantly exceed normal values.
- (3) The possibility that uric acid biosynthesis is augmented in certain gouty subjects has been demonstrated. This is attributed to a biosynthetic shunt at the inosinic acid level, which may be transformed directly to hypoxanthine and uric acid.
- (4) Increased production and increased tubular reabsorption contribute to increase the urate pool.
- (5) The derangement which causes the accumulation of uric acid results in a deposition of urate crystals in the tissues, which is characteristic of chronic gout.
- (6) Acute gout is characterized by an inflammatory reaction of an allergic nature, which cannot be explained by the presence of uric acid crystals in the synovia or by abnormalities of purine metabolism.
- (7) Interference by other metabolic factors (*i.e.* uricolysis by routes not associated with uricase activity) or hormonal reactions (*i.e.* diminished production of gonadal and adrenocortical androgens) appear to be less likely possibilities.

## PART 2. CLINICAL AND THERAPEUTIC STUDIES

BY

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The clinical study which follows is based on 100 cases definitely diagnosed as gout, because of typical acute attacks (in the great toe or in one or more other joints) relieved by colchicine, or because of the presence of tophi.

From the first attack of gout, the disease had lasted:

Less than 10 years in 20 patients  
More than 10 or less than 20 years in 28 patients  
20 years or more in 52 patients

The patients' ages were distributed as follows:

From 30 to 39 years: 1 case  
From 40 to 49 years: 20 cases  
From 50 to 59 years: 45 cases  
From 60 to 69 years: 27 cases  
Over 70 years: 7 cases

#### I. AETIOLOGY

**Sex Ratio.**—Our series of one hundred patients included only four women.

**Family History.**—37 patients knew of at least one

relative who suffered from gout (the father in 22 instances), and four, who were unaware of a family history of gout, had one relative with nephrolithiasis.

**Weight.**—49 patients were overweight.

**Occupation.**—85 followed a sedentary occupation.

**Alcoholism.**—Eighteen were heavy drinkers, taking at least 100 ml. of alcohol daily, mostly in the form of wine.

**Allergy.**—Thirteen had had allergic or reputedly allergic conditions (eczema, urticaria, asthma, hay fever, migraine).

It is doubtful whether the incidence of sedentary occupations, alcoholism, or allergy has any aetiological significance in gout, but the sex ratio and familial incidence of the disease are both highly significant.

## II. ATTACKS

(a) **Precipitating Factors.**—These varied in frequency and were found in 85 patients (Table V). The chief factors incriminated by patients were:

- (i) *Dietetic Errors* (over-eating or consumption of even a moderate quantity of some food item not necessarily rich in purine; alcoholic excess

TABLE V  
IMMEDIATE CAUSES OF ATTACKS OF GOUT

Precipitating Factors	No. of Patients
Diet .. .. .	45
Local Trauma or Repeated Minor Trauma .. ..	43
Physical or Intellectual Overwork .. .. .	34
Cold, Damp .. .. .	23
Psychological Strain .. .. .	21
Infection .. .. .	18
Spa Treatment .. .. .	18
Drugs .. .. .	12
Surgical Operation .. .. .	7
Other Factors (Constipation, Intoxication, Lead Poisoning, etc.) .. .. .	4

or drinking small quantities of a particular alcoholic drink), 45 cases.

- (ii) *Local Trauma*, or repeated minor trauma (walking too far or wearing tight shoes), 43 cases.

- (iii) *Fatigue*, 34 cases.

- (iv) *Emotional Stress* (bereavement, anger, or betrayal), 21 cases.

- (v) *Minor Infections* (sore throat, influenza, bronchitis), 18 cases.

- (vi) *Thermal "Cures"*, certain drugs (especially Probenecid), and various surgical procedures, several cases.

(b) **Prodromal Symptoms** (Table VI).—Seventy patients were warned of an impending attack by local symptoms (slight discomfort at the site of the oncoming attack more than 24 hours before its onset) or by systemic symptoms, mostly nervous (fatigue, insomnia, headache) or digestive (dyspepsia, constipation, diarrhoea). Signs of renal calculus (renal colic or dysuria with a reddish sediment in the urine) sometimes preceded the gouty attack in nine patients.

TABLE VI  
WARNING SYMPTOMS OF ATTACKS OF GOUT

Prodromal Symptoms	No. of Patients
Slight pain at the site of an impending attack .. ..	64
Nervousness, fatigue, insomnia, headache .. ..	41
Dyspepsia, constipation, diarrhoea .. .. .	13
Muscular pains, chills .. .. .	9
Renal colic or dysuria .. .. .	9
Cramp, tingling, and swollen veins in the affected limb	7

(c) **Age.**—Table VII shows the age at the time of the first crisis; 58 had had their first attack of gout between the ages of 30 and 45 years.

(d) **Site.**—Table VIII (opposite) shows the joints involved in the first attack, which nearly always affected the lower limbs (98 per cent.), especially the great toe (78 per cent.). In 67 out of these 78 cases, one great toe only was affected by the first attack. In six of the 100 patients, the first attack was polyarticular, and in two cases only the first attack

TABLE VII  
AGE AT ONSET OF GOUT

Age at Onset of Gout (yrs)	10 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 59	55 to 59	60 and Over
Number of Patients .. ..	0	1	10	13	17	19	22	5	9	4	0

TABLE VIII  
SITES OF FIRST ATTACKS OF GOUT

Joint Involved	Metatarsophalangeal of Great Toe	Joints of the Foot other than the Great Toe and Achilles Tendon	Knee	Ankle	Elbow	Hand	Polyarthritis without involvement of the Great Toe
No. of Patients	78	8	6	3	1	1	3

TABLE IX  
SITES OF ATTACKS OF GOUT DURING THE COURSE OF THE DISEASE

Joint Involved	Great Toe	Other Joints of the Foot	Ankle	Knee	Hip	Fingers	Wrists	Elbow	Shoulder	Cervical Spine	Other
No. of Patients	96	57	63	72	5	37	44	45	12	5	4

affected an upper limb (once the elbow and once a finger).

Table IX shows the joints involved at various times from the date of the first attack until the day of the examination. The first joint of the great toe was almost always affected (96 per cent. of cases), the knee and the ankle very often, the feet (apart from the great toe), elbow, wrist, and fingers often, the shoulders rarely, and the hips, spine, and sternoclavicular joints very exceptionally.

(e) **Clinical Picture.**—The first attack was almost always sudden (94 per cent.) and started at night (62 per cent.). It was usually accompanied by intense local inflammation: swelling and redness (94 per cent.), sharp pain and inability to move from bed or chair (78 per cent.). Dilatation of the adjoining superficial veins often accompanied the gouty swelling (44 per cent.), and even preceded it in a few cases. Almost one-half of the patients had also noted that, at the end of an attack, there was intense itching and desquamation over the joints involved. 62 patients had noticed that their attacks were sometimes, often, or regularly accompanied by fever, which was usually moderate (between 100·4° and 102·2° F.) but sometimes high; ten patients had had a temperature above 102·2° F. and it had occasionally been known to reach 104° F.

A raised erythrocyte sedimentation rate might accompany the fever or occur independently; this finding seemed constant, but the rate varied considerably. In six out of thirty patients in whom it was measured at the height of the attack it was 15-30 mm. in the first hour, in fourteen it was 30-50 mm., in seven it was 50-100 mm., and in three it was above 100 mm.

(f) **Duration of Attack.**—Even the initial attack was not always very short. In two-thirds of our 100

cases it lasted more than 5 days; in one-half more than 10 days; and in one-quarter more than 3 weeks. Attacks lasting more than a month were usually those which affected joints other than the great toe. However, the longer the disease lasted, the more prolonged were the attacks. The first attack usually had no sequelae except slight pains in the feet after a long walk (9 per cent. of cases).

(g) **Atypical Attacks.**

- (i) A mild attack (69 per cent. of our patients had had such attacks).
- (ii) An attack affecting joints other than those of the feet; 68 per cent. of our patients had had one or more such attacks, the most common sites being the knees, ankles, elbows (mainly olecranon bursa), wrists, and finger joints.
- (iii) Acute or sub-acute gouty polyarthritis, usually a late manifestation of gout, was a first symptom in 6 per cent. of cases. It occurred in the course of the disease in 53 per cent. It is apt to be confused with rheumatic fever, but may be distinguished by sudden onset, intense inflammation, accentuation of pain at night, predilection for the lower limbs (the shoulders, hips, spine, temporo-maxillary, and thoracic joints being only rarely involved), and the occurrence of successive bouts which are better described as a series of mono-articular attacks than as a true polyarthritis. Usually, though not always, it is characterized by slow development and relative resistance to the commoner anti-gouty measures.

(h) **Differential Diagnosis.**—The first attack of gout, (and sometimes even subsequent ones) is often wrongly diagnosed. In our series of 100 patients,



only 63 were correctly diagnosed from the start; the rest were thought to be suffering from rheumatism, infective arthritis, abscess, articular trauma, etc.

### III. CHRONIC GOUTY ARTHRITIS

(a) **Tophi.**—Tophaceous gout was found in 59 of our 100 patients. This high proportion is probably due to the fact that most of them were long-standing cases of gout. Tophi are seen more frequently as the duration of the disease increases. We found no tophi in those who had had the disease for less than 5 years, whereas tophi were seen in 70 per cent. of those who had had gout for more than 20 years. Tophi usually appear after the tenth year, but may develop earlier, and in exceptional cases may even antedate the first attack of gout (2 per cent. in our series). The most frequent sites of tophi (Table X) are the outer ears, hands, feet, elbows, and knees, in that order. Eleven patients had tophi only on the ears, and four only on the elbows. The tophi are often the site of acute inflammatory swellings, and these were seen in 30 of our 59 patients. Tophi rarely resorb, except occasionally on the outer ears. They frequently become ulcerated, and this was seen in eighteen patients in the course of the disease.

TABLE X  
SITES OF TOPHI

Site of Tophus	Ears	Hands	Feet	Elbows	Knees
No. of Cases ..	36	32	27	24	5

(b) **Chronic Gouty Arthropathy (Gouty Arthritis).**—Frequently, after 10 years, but more often after 20 years, gout may cause chronic joint pain, which mainly involves the feet (55 per cent.), but may also affect the wrists and fingers (40 per cent.), thus sometimes mimicking the clinical picture of rheumatoid arthritis. When the knees are involved (29 per cent.), gouty arthritis may resemble osteo-arthritis.

### IV. RENAL CALCULUS

Twenty-two of our patients had had one or more attacks of renal colic, not counting five in whom the attack was precipitated by a uricosuric drug. Many of those who did not have colic reported the occasional appearance of a reddish sediment in the urine.

### V. RENAL DYSFUNCTION IN GOUTY PATIENTS

Renal function tests were carried out in 75 patients. Albuminuria was found in eight (of which four had no renal insufficiency), azotaemia of more than 50 mg./100 ml. in ten, and slight renal insufficiency

without azotaemia (as demonstrated by a figure of less than 50 per cent. in the Van Slyke clearance test) in nine. The somewhat incomplete renal examination which we made showed evidence of renal dysfunction in 23 out of 75 patients. Impairment of renal function was more common in tophaceous gout (14 out of 49 cases), than in the non-tophaceous variety, where it was seen in five cases out of 33. It was also much more frequent in those in whom gout was associated with urinary lithiasis.

### VI. OTHER SYSTEMIC DISEASES

In 28 patients the systolic blood pressure was above 160 mm. Hg, and in nine it exceeded 200 mm. Hg. Six had symptoms of coronary insufficiency (two with myocardial infarction and four with anginal pain only). Thirteen had gastric trouble, three had stomach ulcers, thirteen had colitis, and seven had bladder stones. It is not certain, however, that these numbers are higher than would be found in 100 non-gouty subjects of the same age and weight.

### VII. BIOCHEMICAL DATA

In 96 per cent., the serum uric acid levels (direct colorimetric method) were above 6 mg./100 ml. in one or more tests, 32 out of 57 had serum cholesterol values above 200 mg./100 ml. Four out of 100 had moderate glycosuria. Serum calcium estimations in 23 patients between attacks always gave normal readings.

### VIII. DISABILITY

Gout is a crippling disease, and apart from the incapacity caused by repeated acute attacks, the progression of the chronic arthropathy eventually leads to permanent invalidism.

61 of our patients had some chronic disability, especially in walking. Nine of these 61 were able to work only irregularly and nine others were quite incapacitated; twelve of these eighteen patients had suffered from gout for more than 20 years.

### IX. RADIOLOGICAL FINDINGS

The chief changes are cystic destruction of bones due to urate deposition and characteristically described as punched-out areas of bone, narrowing of the joint spaces, and the development of osteophytes around the joints. Diffuse decalcification is also observed in prolonged attacks, particularly in the feet and hands; 66 out of 80 patients had x-ray lesions in the feet or hands, or both, and in 53 of these the lesions were plainly cystic (punched-

out). Table XI shows that punched-out areas are particularly common in patients suffering from tophaceous gout.

TABLE XI  
RADIOLOGICAL LESIONS IN HANDS AND FEET  
IN 80 CASES

Radiological Lesions found in Hands and Feet	Type of Gout				Total	
	Non-Tophaceous (35 Cases)		Tophaceous (45 Cases)			
	No.	Per cent.	No.	Per cent.	No.	Per cent.
None .. .. .	8	22.8	6	13.3	14	17.5
Slight .. .. .	11	31.4	2	4.9	13	16.2
Definite with punched-out areas .. .. .	16	45.7	37	82.2	53	66.2
Total .. .. .	35		45		80	

(a) Feet.—The most frequent radiological appearances were the following:

- (i) Changes in the metatarso-phalangeal joints of the great toe. These were seen in one or both feet in 59 cases out of eighty. The lesions take the form of well-defined, punched-out areas at the ends of the bones, narrowing of the joint spaces, osteophytosis, and (a very frequent sign) antero-posterior hypertrophy with an irregularly increased translucency of the sesamoid bones adjacent to the joints.
- (ii) Bristling osteophytes of the superior aspects of the tarsal joints were seen in one or both feet in 51 cases out of eighty.
- (iii) Osteophytosis of the heel, both below and behind the calcaneus, was seen in 49 cases out of eighty.

(b) Hands and Wrists.—Lesions were seen in 41 cases out of 80; the most frequent findings were the following:

- (i) Lesions of the fingers, cystic or otherwise (39 out of eighty).
- (ii) Radio-carpal lesions, usually with punched-out areas (27 out of eighty).
- (iii) Cystic lesions of the carpal bones (23 out of eighty).

(c) Knees.—Of 29 gouty subjects with clinical involvement of the knees, 21 showed osteophytic lesions; although these resembled ordinary osteoarthritis, they often showed notches and gaps near or within the substance of the osteophytes themselves. Six cases showed calcification of the insertion of the patellar tendon.

(d) Elbows.—The most characteristic lesions were the shadows of tophi, which were visible in the soft

tissue, and osteophytes of the coronoid process along the insertion of the triceps tendon, associated with erosion of the coronoid.

X. THERAPY

(a) Treatment of Acute Attacks.

(1) Colchicine.—Out of 76 patients who tried oral colchicine, 45 had excellent results, twelve had good results in slight attacks, and nineteen had poor results. No serious side-effects were observed, but digestive intolerance was frequent and was the usual reason for failure. Intravenous colchicine, which was given to fourteen of our patients, gave better and more rapid results than oral colchicine, the benefit being felt 3 or 4 hours after the injection of 3 mg. of the drug. Local venous reactions were observed in five out of fourteen patients.

(2) Phenylbutazone.—About 300 attacks in 89 patients were treated with phenylbutazone. The parenteral route seemed to give the best results, 1 g. being injected intravenously directly symptoms appeared, 1 g. intramuscularly the next day or the day after, and 1 g. intramuscularly on the fifth day. In 92 per cent. of cases, the attack was aborted in a few hours, mostly within 2 hours. Thus employed, phenylbutazone seems superior to all other drugs.

Patients with visceral lesions, and those with hepatic, cardiac or blood disorders, should be excluded, and all the patients must be placed on a salt-free diet (otherwise oedema may supervene: three cases). We had four cases of haemorrhage (one with haematemesis, one with intestinal haemorrhage, and two with epistaxis). Also, phenylbutazone may cause epigastric pain (ten patients out of 89) and renal colic in those suffering from renal calculi.

(3) Adrenocortical Hormones.—Large doses (25 mg. prednisone daily or more) gave very satisfactory results in thirteen out of seventeen patients. In two cases, epigastric pain caused the treatment to be withdrawn. With smaller doses (less than 25 mg. prednisone daily) only eight out of eighteen patients had a good result.

(4) Aspirin.—Of 32 patients who were treated with aspirin alone, in doses of 4 g. daily or more, sixteen (50 per cent.) said that they were satisfied with the results, but, generally speaking, aspirin is only sufficient in slight or moderate attacks.

(5) Atophan (Cincophen).—Nearly all those patients who were given this drug (in small doses of only 1.5 g. daily for a few days) said that it had little effect on the attack.

**(b) Systemic Treatment.**

(1) *Diet.*—The patients' answers to our interrogation did not lend themselves to the formation of an opinion on this subject. During the war period, when the diet of most of the French population was severely restricted, fifteen out of 46 patients had no attack, and in fifteen others the frequency of the attacks diminished. A low diet, therefore, was extremely efficacious in thirty cases out of 46. This finding is quite remarkable, but it is difficult to detect which of the dietary or other restrictions imposed during the war was responsible for the undoubted improvement experienced by many of our patients.

(2) *Phenylbutazone.*—41 patients were given daily maintenance doses of 100-200 mg. phenylbutazone. In ten the drug had to be withdrawn on account of side-effects, usually digestive, and the other 31 followed this course of treatment for 3 or 4 years. In twenty out of the 31 who had previously experienced frequent acute episodes of gout, the attacks were prevented in six cases, diminished in six, and unchanged in eight. Eleven of the 31 had a chronic arthropathy; six obtained some relief from symptoms, but in the other five relief was either transient or non-existent. Intra-articular injections of 400 mg. phenylbutazone gave striking results in several cases where an acute inflammatory episode had supervened in gouty arthritis of the knees.

(3) *Benemid (Probenecid).*—This was prescribed to 89 patients, 1 g. daily. Nine showed intolerance of the drug (six digestive and three cutaneous). In ten others treatment had to be stopped because of renal colic, but an old history of nephrolithiasis was found in nine of them. Twelve stopped treatment because of an attack of gout which was apparently precipitated by the drug. This shows the necessity of starting this treatment simultaneously with colchicine or phenylbutazone. Thirty patients received probenecid for less than 6 months, and in 28 patients, who were treated for periods ranging from 6 months to 3 years, the results were as follows:

- (i) Reduction of frequency or absence of attack in sixteen.
- (ii) Improvement in the symptoms of gouty arthritis in seven out of fourteen.
- (iii) Regression of tophi (disappearance of one ear tophus and diminution of digital tophi) was observed in two cases, and no tophus ever started to form during treatment.

(4) *Long-Term Therapy with Colchicine and Salicylates.*—Our impressions of prolonged colchicine therapy are favourable, but our experience has not yet been long enough for any firm conclusion to be drawn. Salicylate therapy in doses of not less than

4 g. per day, combined with an equal quantity of sodium bicarbonate, nearly always caused digestive upsets, and could only be given for a few weeks.

**SUMMARY OF PART TWO**

A clinical and therapeutic study has been made of 100 cases of gout (96 men and 4 women) diagnosed by the occurrence of typical sharp attacks which could be mitigated by colchicine, or by the presence of tophi. The patients' ages ranged from 30 to over 70 years. The family history, precipitating factors, prodromal symptoms, and clinical picture were reviewed. Tophi, gouty arthritis, systemic disease, and degree of disability were investigated, and detailed radiological examinations were carried out.

The most rapid, striking, and spectacular results in the treatment of acute attacks of gout were obtained with phenylbutazone. Colchicine by mouth is effective in treating an acute attack, provided it is given at the first onset of symptoms. Prednisone is usually efficacious if it can be given in relatively large doses. Aspirin is of little use except in slight attacks.

As far as the systemic treatment of chronic gout is concerned, a restricted diet, judging from the experience of patients in the war period from 1941 to 1945, gave excellent results in 32 per cent. of cases.

Probenecid seems to be a promising remedy for both acute and chronic gout, but should be used, at least initially, in combination with phenylbutazone or colchicine.

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(3) L'hypothèse que la biosynthèse de l'acide urique serait augmentée chez certains goutteux a été prouvée. On attribue ceci à un shunt biosynthétique au niveau de l'acide inosinique qui peut se transformer directement en hypoxanthine et en acide urique.

(4) La production et la réabsorption tubulaire accrues contribuent à augmenter la "pool" uratique.

(5) Le dérangement provoqué par l'accumulation d'acide urique aboutit au dépôt de cristaux d'urate dans les tissus, ce qui caractérise la goutte chronique.

(6) La goutte aiguë est caractérisée par une réaction inflammatoire de nature allergique, qui ne peut pas être expliquée par la présence de cristaux d'acide urique dans la synoviale ou par des anomalies du métabolisme des purines.

(7) L'intervention d'autres facteurs, métaboliques (tels que l'uricolyse par des voies non associées à l'action de l'uricase) ou hormonaux (tels que la production diminuée d'androgènes gonadaux ou surrénocorticaux) semble moins probable.

## Deuxième Partie: Etudes cliniques et thérapeutiques

On a fait une étude clinique et thérapeutique de 100 cas de goutte (96 hommes et 4 femmes), diagnostiqués ou par de violentes attaques typiques, susceptibles d'être calmées par la colchicine, ou par la présence de tophi. L'âge des malades allait de 30 à plus de 70 ans. On passe en revue les antécédents de famille, les facteurs précipitants, les symptômes de début et le tableau clinique. On a étudié les tophi, l'arthrite goutteuse, les maladies intercurrentes, le degré d'incapacité, et on a fait des examens radiologiques détaillés.

Les résultats les plus rapides, frappants et spectaculaires dans le traitement des attaques aiguës de goutte furent obtenus avec la phénylbutazone. La colchicine par voie buccale est efficace pourvu qu'on l'administre dès les premiers symptômes. La prednisone est efficace en doses relativement hautes. L'aspirine n'est utile que dans les attaques légères.

En ce qui concerne le traitement général de la goutte chronique, un régime restreint, à en juger d'après l'expérience acquise avec des malades de la période de guerre de 1941 à 1945, donna d'excellents résultats dans 32% des cas.

Le probénécide (bénévide) semble un médicament prometteur à la fois contre la goutte aiguë et chronique, mais il doit être employé, du moins au début, en combinaison avec la phénylbutazone ou la colchicine.

## Fisiopatología, manifestaciones clínicas, y tratamiento de la gota. Investigación de 100 casos

### Primera Parte: Fisiopatología y patogénesis

#### SUMARIO

Aún falta mucho para completar nuestros conocimientos de la patogénesis de la gota, pero las descubiertas muy recientes, así como nuestros propios resultados, permiten sacar las conclusiones siguientes:

(1) En la gota hay una aumentación del "pool miscible" de uratos (cantidad global de ácido úrico en la circulación).

(2) Una reabsorción tubular acrecentada de ácido úrico y una eliminación urática disminuida se ven en los gotosos, aun cuando la cantidad de urato excretado no rebasa significativamente las cifras normales.

(3) La posibilidad de que la biosíntesis del ácido úrico en ciertos sujetos gotosos estuviera aumentada ha sido comprobada. Se atribuye esto a un shunt biosintético

## Physiopathologie, manifestations cliniques, et traitement de la goutte. Etude portant sur 100 goutteux

### Première Partie: Physiopathologie et pathogénie

#### RÉSUMÉ

La pathogénie de la goutte est loin d'être complètement connue, mais les découvertes les plus récentes, ainsi que nos propres résultats, permettent de tirer les conclusions suivantes:

(1) Dans la goutte, il y a une augmentation du "pool miscible" d'urates (quantité globale d'acide urique en circulation).

(2) Une réabsorption tubulaire accrue d'acide urique et une élimination uratique diminuée existent chez les goutteux, même quand la quantité d'urate excrétée ne dépasse pas appréciablement les chiffres normaux.



al nivel del ácido inosínico que se puede transformar directamente en hipoxantina y en ácido úrico.

(4) La producción y la reabsorción tubular acrecentadas contribuyen a aumentar el "pool" urático.

(5) El desarreglo provocado por la acumulación de ácido úrico acaba en el depósito de cristales de urato en los tejidos, lo que caracteriza la gota crónica.

(6) La gota aguda se caracteriza por una reacción inflamatoria de naturaleza alérgica, que no se puede explicar por la presencia de cristales de ácido úrico en la sinovia o por anomalías del metabolismo de las purinas.

(7) La intervención de otros factores, sea metabólicos (tales como la uricolisis por vías no asociadas a la acción de la uricase), sea hormonales (como la producción disminuida de andrógenos gonadales o suprarrenocorticales), parece menos probable.

#### Segunda Parte: Estudios clínicos y terapéuticos

Se estudiaron clínica y terapéuticamente 100 casos de gota (96 hombres y 4 mujeres), diagnosticados sea por violentos ataques típicos susceptibles de mitigación por

la colchicina, sea por la presencia de tofos. La edad de los enfermos fué entre 30 y 70 años. Se pasa en revista a los antecedentes familiares, los factores precipitantes, los prodromos y el cuadro clínico. Tofos, artritis gotosa, enfermedades intercurrentes y grado de incapacidad fueron investigados, con la ayuda de exámenes radiológicos detallados.

Los resultados más rápidos y asombrosos en el tratamiento de los ataques agudos de gota fueron obtenidos con fenilbutazona. La colchicina por vía oral es eficaz, provisto que se la administra tan pronto como aparecen los síntomas. La prednisona es eficaz en dosis relativamente altas. La aspirina es útil sólo en ataques ligeros.

En cuanto al tratamiento general de la gota crónica, un régimen de restricción alimenticia, á juzgar por la experiencia con enfermos durante la guerra de 1941 á 1945, dió excelentes resultados en un 32% de los casos.

El probenecid (benemid) parece ser un medicamento prometedor, tanto contra la gota aguda como la crónica, pero se debe emplearle, al menos al principio, en combinación con la fenilbutazona o la colchicina.

## TRANSFORMATION OF COLLAGEN TO "ELASTIN" IN DERMAL COLLAGENS WITH VARYING SENSITIVITY TOWARDS COLLAGENASE

BY

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It has been reported previously (Keech, 1955) that the dermal collagen from eight out of sixty individuals failed to show any evidence of digestion by collagenase under the electron microscope, and that two others reacted excessively for their particular age groups. Indications of variable reactivity towards collagenase were also obtained from nitrogen determinations of the material digested (Keech, 1954a). It was also shown that in one case of dermatomyositis the rash-bearing skin was collagenase-resistant, whereas the abdominal skin from the same case digested normally. All these findings remained unexplained and appeared to be independent of the disease, therapy, and all the experimental procedures.

A small quantity of eight out of the ten abnormally-reacting substrates still remained, so a more detailed electron microscope investigation was undertaken to find out whether the samples shown to be resistant to the action of collagenase would also prove resistant to the action of alkali and periodate which apparently transforms collagen to elastin-like structures (Burton, Hall, Keech, Reed, Saxl, Tunbridge, and Wood, 1955; Hall, Keech, Reed, Saxl, Tunbridge, and Wood, 1955). Microshrinkage temperature experiments were performed as well as analytical studies on the amino acid composition of the various samples. More detailed characterization was accomplished by chromatography and hydroxyproline determinations.

### Materials and Methods

**Prepared Collagen.**—Six of the eight collagenase-

resistant substrates and the two exhibiting excessive digestion which were used in previous work (Keech, 1955), together with five controls of comparable age showing average collagenase digestion, constituted the starting materials. Each was examined as described below and then treated in one of the following ways:

- (a) Suspended in sterile distilled water pH 5.6, heated at 37° C., and samples taken after 1½, 3, and 24 hrs.
- (b) Suspended in 0.2 M potassium hydrogen phthalate buffer, pH 5.0, heated at 37° C., and samples taken after 1½ and 3 hrs.
- (c) Suspended in a mixture of 1 per cent. sodium metaperiodate in phthalate buffer, pH 5.0, incubated at 37° C., and samples taken at 1½ and 3 hrs.
- (d) Suspended in 0.2 M borate buffer, pH 8.8, and incubated at 37° C. for 24 hrs.

**Antibiotics.**—0.05 ml. of a penicillin and streptomycin mixture was added to each test tube in the above experiments. This successfully prevented bacterial contamination.

**Samples for Electron Microscopic Examination** were ground gently in a glass tissue grinder until a milky suspension was obtained; drops were placed on collodion-covered 200-mesh copper grids, drained with filter paper, allowed to dry, washed with distilled water, shadowed with chromium, and examined in a Siemens electron microscope, type UM 60 C.

Counts of the different elastin-like structures were made by carefully scanning two grids from each sample. The specimen holder had been adjusted to visualize 25 squares of the grid, and each part of each square was examined in sequence. As each square was scanned at a magnification of 11,000 and as about 25 fields were needed to cover each square, a *minimum* of 2 × 625 fields were scrutinized from each specimen.

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Attempts were made to obtain approximately the same amount of deposit on all the grids from all the samples, so that valid comparisons could be made. This proved difficult, but the majority of the grids were classified as bearing a "heavy" deposit, and where variations in density affect comparisons in the counts, this has been indicated in both Tables and text.

The above experiments were performed in large batches, treating several different substrates from each group in each of the ways described at the same time. This ensured that exactly the same conditions (chemical solutions, incubation temperature, etc.) appertained to the reactive and resistant materials alike. Again, electron microscope examination of all the experiments on the same substrate were undertaken within 2 to 3 days, for ease of comparison.

**Terminology.**—The presence of several types of "elastin" in the materials used in this study is somewhat confusing. For clarity they were classified as follows:

(a) Naturally-occurring elastin or fully-formed elastin (Fig. 14) as described previously (Keech, Reed, and Wood, 1956) comprising three variants (skin-type, filamenting, and natural networks) which are found in fresh whole dermis and prepared dermis from all age groups, aorta, tendon, and ox ligamentum nuchae. This appears in the text without quotation marks. The term *fully-formed elastin* bears no genetic implication, but simply indicates that it is found in all fresh and prepared starting materials.

(b) Morphologically similar structures, seen after a variety of procedures, are referred to as *fully-formed "elastin"* or *elastin-like structures*. There is much evidence that these structures resemble the naturally-occurring elastin described under (a) in chemical properties as well as in morphology (Burton and others, 1955; Hall and others, 1955). However, until this point is fully established, quotation marks are used.

(c) A larger form, composed of a very thick, dense portion splaying out into typical skin-type or filamenting elastin (Figs 26-35). These frequently stretched over several microscopic fields, measured 20-30 $\mu$  in length, and formed a distinct group which proved the most sensitive index of a true transformation picture (see below). The term *transformation structure* (TS) is used for this group, implying that they exhibit one or more of the various morphological characteristics of "elastin". As already reported (Keech and Reed, 1957), large, dense, square-ended fibres are present in all the starting materials of both fresh whole dermis as well as the prepared substrates. As shown in the published illustrations, prolonged heat at or below body temperature gradually converted some of these fibres into TS, their appearance depending on the amount of electron-opaque amorphous material coating the elastin filaments. However, they were found in far greater numbers following the reagents (borate, periodate and phthalate) used in the present study.

A *transformation picture* (Figs 36 and 37) denotes,

therefore, a quantitative and qualitative change in the whole deposit, characterized by:

- (i) A smaller amount of collagen, the majority of which showed evidence of degeneration;
- (ii) An increase in skin-type "elastin" above that which could be accounted for by heat alone;
- (iii) An increase in TS (or in large networks in the substrate from the infant D12: see Table I).

Qualitatively, the appearance of the deposit was quite distinctive, the elastin-like material covering most of the grid in the samples recorded as presenting a marked transformation picture.

The word "transform" is thus used to denote the apparent transformation of collagen to elastin-like structures reported previously (Burton and others, 1955; Keech and Reed, 1957) as well as in the present study. The term "transformation structure" (TS) was first used to describe the conversion of the large, dense fibres present in the starting materials to "elastin" (Keech and Reed, 1957). The same name is now used for the identical structures found in greater numbers in the present investigation. A "transformation picture" (defined above) refers to a change in the whole deposit, the mainly collagenous starting material being replaced by elastin-like structures. Part of this change was accomplished by the conversion of the large, dense fibres to TS.

It is important to make it quite clear that the terms defined above are used descriptively and as an aid in classifying the range of structures counted and recorded in Tables I and II. They are *not* intended to imply any underlying mechanism or biological process.

## Results

The results are summarized in Tables I to III, where Group I comprises substrates exhibiting average collagenase digestion, Group II comprises collagenase-resistant substrates, and Group III comprises those showing excessive digestion by collagenase.

### Starting Materials (Figs 1-8)

These showed marked differences between each group, as well as age differences within Group I, the latter giving the typical pictures of child and adult prepared dermis. In the younger subjects the slightly thinner collagen fibrils were usually found in clumps, mixed with, or partially obscured by, the plentiful amorphous material and dense bits. In contrast, the collagen in a 56-year-old adult was in long, winding bundles of clean fibrils with very little associated amorphous material or dense bits. The substrate from the infant (D12) contained nearly as much filamenting as skin-type elastin (a common finding in very young subjects), whereas filamenting formed only a small fraction of the total

fully-formed elastin in the rest. In addition many structures were intermediate between the four variants of elastin listed in Table I, but (as has been noted in previous work) the action of heat alone, or

heat plus other reagents, rapidly rendered them typical of one particular variant and hence easy to categorize. The 56-year-old dermis (D15) had scanty, long, thick pieces of filamenting elastin which

TABLE I

RESULTS OF VARIOUS TREATMENTS TO PREPARED DERMAL SUBSTRATES WHICH DIFFERED IN SENSITIVITY TOWARDS COLLAGENASE

AT LEAST 1,250 MICROSCOPIC FIELDS WERE EXAMINED AT EACH TIME-INTERVAL

GROUP I. SUBSTRATES EXHIBITING AVERAGE COLLAGENASE DIGESTION (CONTROL GROUP)

Substrate and Treatment (hrs)		Fully-Formed Elastin			TS	Fine Threads	Dense Bits	Amorphous Material	Grid Deposit	Collagen	Elastin	Remarks
		S	F	N								
D12 20 mths (Normal Control)												
D12 <sub>1</sub> Starting Material in H <sub>2</sub> O		53	39	4	34	V.Sc.	Num.	Mod.	H	Typical child substrate. In clumps with AM and DB	Difficult to categorize as many intermediate forms. Mostly small pieces counted	
D12 <sub>5</sub> Heat only in H <sub>2</sub> O at 37° C.	1½	138	13	11	38	Mod.	Num.	Mod.	H	Mostly unaltered	Majority counted were tiny pieces	No TP
	3	259	2	3	19	V.Sc.	Num.	Mod.	H	Mostly unaltered	Majority counted were tiny pieces Only small TS	No TP
	24	637	10	28	86	Sc.	Num.	Mod.	VH	Fair amount starting to degenerate	Large TS V. large networks and long pieces F	Marked TP
D12 <sub>3</sub> Buffer (pH 5.0)	3	301	20	85	90	Sc.	Num.	Mod.	MH	Fair amount starting to degenerate	* See footnote	Marked TP
D12 <sub>4</sub> Periodate (pH 5.0)	3	397	16	55	93	V.Sc.	Num.	Mod.	H	Fair amount starting to degenerate	* See footnote	Marked TP
D12 <sub>2</sub> Buffer (pH 8.8)	24	286	52	3	91	V.Sc.	Num.	Inc.	H	Some starting to degenerate	No large "networks". Some mod. large TS	Mod. TP. Not as marked as D12 <sub>3</sub> and D12 <sub>4</sub>
D13 9 yrs (Normal Control)												
D13 <sub>1</sub> Starting Material in H <sub>2</sub> O		86	6	7	29	V.Sc.	Num.	Mod.	H	Typical child substrate. In clumps with AM and DB	N of mod. size	
D13 <sub>5</sub> Heat Only in H <sub>2</sub> O at 37° C.	1½	130	14	7	39	Sc.	Num.	Mod.	H	Mostly unaltered		No TP
	3	160	7	—	14	Sc.	Num.	Mod.	H	Mostly unaltered	Nearly all small or mod. in size	No TP
	24	168	16	1	53	Sc.	Num.	Mod.	H	Mostly unaltered		No TP
D13 <sub>3</sub> Buffer (pH 5.0)	3	469	10	21	108	Sc.	Num.	Mod.	H	Some starting to degenerate	Many large TS. Most of the N were of mod. size	Marked TP
D13 <sub>4</sub> Periodate (pH 5.0)	3	470	15	8	56	V.Sc.	Num.	Mod.	H	Some starting to degenerate	Nearly all small or mod. in size	Not such a marked TP as D13 <sub>3</sub>
D13 <sub>2</sub> Buffer (pH 8.8)	24	321	32	20	109	Mod.	Num.	Inc.	H	Some starting to degenerate	Several large TS and a few networks as in D12	Mod. TP

continued—



TABLE I (continued)

<b>D14 19 yrs (Normal Control)</b>												
D14 <sub>1</sub> Starting Material in H <sub>2</sub> O	219	23	24	87	V.Sc.	Num.	Mod.	H	In clumps mixed with AM and DB	Nearly all small or mod. in size	A few large TS	
D14 <sub>5</sub> Heat Only in H <sub>2</sub> O at 37° C.	1½	208	11	8	66	Sc.	Num.	Mod.	H	Mostly unaltered	Nearly all small or mod. in size	Like starting material. No TP
	3	268	10	3	57	Mod.	Num.	Mod.	H	Mostly unaltered	Nearly all small or mod. in size	No TP
	24	183	5	4	96	V.V.Sc.	Num.	Mod.	H	Mostly unaltered	Nearly all small or mod. in size	No TP
D14 <sub>3</sub> Buffer (pH 5·0)	1½	Not done										
D14 <sub>4</sub> Periodate (pH 5·0)	1½	Not done										
D14 <sub>3</sub> Buffer (pH 5·0)	3	380	7	5	135	V.Sc.	Num.	Mod.	H	Some starting to degenerate	Inc. in large TS	Marked TP
D14 <sub>4</sub> Periodate (pH 5·0)	3	361	3	5	95	V.Sc.	Num.	Mod.	H	Some starting to degenerate	Not so many large TS	Mod. TP
D14 <sub>2</sub> Buffer (pH 8·8)	24	362	14	3	123	Mod.	Num.	Inc.	H	Some starting to degenerate	Inc. in mod. sized TS	Mod. TP
<b>D5 43 yrs (Normal Control)</b>												
D5 <sub>1</sub> Starting Material in H <sub>2</sub> O	67	1	1	18	None	Few	Mod.	VH	In clumps mixed with AM	Majority counted were tiny pieces		
D5 <sub>5</sub> Heat Only in H <sub>2</sub> O at 37° C.	1½	176	2	—	28	None	Mod.	Mod.	VH	Mostly unaltered	Majority counted were tiny pieces	No TP
	3	350	2	—	35	None	Mod.	Mod.	VH	Mostly unaltered	Majority counted were tiny pieces	No TP
	24	109	—	—	21	V.Sc.	Less	Less	MH	Mostly unaltered	Majority counted were tiny pieces	No TP Lighter deposit
D5 <sub>3</sub> Buffer (pH 5·0)	1½	243	2	1	36	None	Mod.	Mod.	H	Mostly unaltered	Some large TS	Mod. TP
D5 <sub>4</sub> Periodate (pH 5·0)	1½	254	1	—	60	None	Mod.	Mod.	H	Mostly unaltered	Some large TS	Mod. TP
D5 <sub>3</sub> Buffer (pH 5·0)	3	403	11	1	86	V.Sc.	Mod.	Mod.	H	Mostly unaltered	Some large TS	Mod. TP
D5 <sub>4</sub> Periodate (pH 5·0)	3	121	1	—	17	None	Mod.	Mod.	H	Mostly unaltered	Like starting material	Unexpected picture
D5 <sub>2</sub> Buffer (pH 8·8)	24	348	6	2	49	V.Sc.	Mod.	Mod.	VH	Mostly unaltered	Many tiny pieces Some v. large TS	Mod. TP
<b>D15 56 yrs (Normal Control)</b>												
D15 <sub>1</sub> Starting Material in H <sub>2</sub> O	128	16	6	28	Sc.	Few	Sc.	H	"Adult type" unaltered collagen often in bundles	Tiny pieces S. Long thick pieces F. Scanty, small atypical TS		
D15 <sub>5</sub> Heat Only in H <sub>2</sub> O at 37° C.	1½	181	9	4	41	V.Sc.	Mod.	Mod.	H	Mostly unaltered	Small or mod. sized typical TS	Like starting material. No TP
	3	202	4	3	47	V.Sc.	Mod.	Mod.	H	Mostly unaltered	A few mod. large TS	No TP
	24	244	21	9	57	Sc.	Mod.	Mod.	H	Mostly unaltered	Inc. in small and mod. sized S	No TP
Buffer (pH 5·0)	1½	Not done										
Periodate (pH 5·0)	1½	Not done										
D15 <sub>3</sub> Buffer (pH 5·0)	3	296	10	1	27	V.Sc.	Mod.	Mod.	H	Mostly unaltered	Inc. in small and mod. sized S	No TP
D15 <sub>4</sub> Periodate (pH 5·0)	3	318	4	3	39	V.Sc.	Mod.	Mod.	H	Mostly unaltered	Mod. large typical TS	No TP
D15 <sub>2</sub> Buffer (pH 8·8)	24	280	17	3	34	Sc.	Inc.	Inc.	H	Mostly unaltered	Inc. in small and mod. sized S	No TP

TABLE I (continued)

## GROUP II. SUBSTRATES EXHIBITING COLLAGENASE RESISTANCE

Substrate and Treatment (hrs)		Fully-Formed Elastin			TS	Fine Threads	Dense Bits	Amorphous Material	Grid Deposit	Collagen	Elastin	Remarks
		S	F	N								
D8 19 mths (Indigestible)												
D8 <sub>1</sub> Starting Material in H <sub>2</sub> O	70	7	—	12	None	Few	Mod.	H	"Adult type", mostly clean, in bundles and unaltered	Nearly all L	Very unlike usual baby substrate	
D8 <sub>5</sub> Heat Only in H <sub>2</sub> O at 37° C.	1½	Not done										
	3	99	9	5	34	V.Sc.	V. few	Sc.	MH	Same as starting material	Inc. in large TS and some large N	No true TP
	24	87	3	—	29	None	V. few	Sc.	MH	Same as starting material	Some mod. large TS	No true TP
D8 <sub>3</sub> Buffer (pH 5·0)	3	169	2	2	115	None	Few	Sc.	H	Some in clumps or starting to degenerate	Marked inc. in large TS	Marked TP
D8 <sub>4</sub> Periodate (pH 5·0)	3	64	2	2	24	V.V.Sc.	Few	Sc.	MH	Some in clumps or starting to degenerate	Less than D8 <sub>3</sub>	Slight TP
D8 <sub>2</sub> Buffer (pH 8·8)	24	35	3	—	27	V.Sc.	Inc.	Mod.	MH	Some in clumps or starting to degenerate		No TP
D11 5½ yrs (Indigestible)												
D11 <sub>1</sub> Starting Material in H <sub>2</sub> O	57	—	—	36	None	Few	Mod.	H	"Adult type", mostly clean, in bundles and unaltered	Mod. number of TS		
D11 <sub>5</sub> Heat Only in H <sub>2</sub> O at 37° C.	1½	Not done										
	3	88	2	—	60	V.Sc.	Few	Mod.	H	Same as starting material	Inc. in mod. large TS	No true TP
	24	114	3	—	65	V.Sc.	Few	Mod.	H	Same as starting material		No true TP
D11 <sub>3</sub> Buffer (pH 5·0)	3	58	1	—	28	None	Few	Mod.	H	Same as starting material		No true TP
D11 <sub>4</sub> Periodate (pH 5·0)	3	85	2	—	44	None	Few	Mod.	H	Same as starting material	Nearly all tiny pieces	No true TP
D11 <sub>2</sub> Buffer (pH 8·8)	24	132	1	1	71	None	Inc.	Inc.	VH	Same as starting material	Inc. in large TS	VH deposit No true TP
D9 9½ yrs (Indigestible)												
D9 <sub>1</sub> Starting Material in H <sub>2</sub> O	41	—	—	16	None	V. few	V.Sc.	H	"Adult type", clean, in bundles and unaltered		Very similar to D10	
D9 <sub>5</sub> Heat Only in H <sub>2</sub> O at 37° C.	1½	Not done										
	3	87	5	—	30	V.Sc.	V. few	V.Sc.	H	Same as starting material		No TP
	24	51	1	—	43	V.Sc.	V. few	V.Sc.	MH	Same as starting material	Increase in TS some quite large	Lighter deposit No TP
D9 <sub>3</sub> Buffer (pH 5·0)	3	101	2	—	64	V.V.Sc.	V. few	Sc.	H	Same as starting material	Inc. in mod. sized TS and S	Mod. TP
D9 <sub>4</sub> Periodate (pH 5·0)	3	57	3	—	25	V.V.Sc.	V. few	Sc.	MH	Same as starting material		Lighter deposit Slight TP
D9 <sub>2</sub> Buffer (pH 8·8)	24	60	1	—	28	V.Sc.	Few	Sc.	MH	Same as starting material		No TP

continued—

TABLE I (continued)

D10 13 yrs (Indigestible)											
D10 <sub>1</sub> Starting Material in H <sub>2</sub> O ..	23	3	—	10	None	V. few	V.Sc.	H	"Adult type", clean, in bundles and unaltered		Very similar to D9
D10 <sub>5</sub> Heat Only in H <sub>2</sub> O at 37° C.	1½	Not done									
	3	27	2	—	15	None	V. few	V.Sc.	H	Same as starting material	No TP
	24	51	3	—	19	None	V. few	V.Sc.	H	Same as starting material	Inc. in S No TP
D10 <sub>3</sub> Buffer (pH 5·0)	3	28	—	—	19	None	V. few	V.Sc.	H	Same as starting material	Nearly all tiny pieces No TP
D10 <sub>4</sub> Periodate (pH 5·0)	3	21	—	—	15	None	V. few	V.Sc.	MH	Same as starting material	No TP
D10 <sub>2</sub> Buffer (pH 8·8)	24	79	—	—	27	None	Few	Sc.	H	Same as starting material	Nearly all L. No TP
D4 18 yrs (Indigestible)											
D4 <sub>1</sub> Starting Material in H <sub>2</sub> O ..	21	1	—	13	None	V. few	V.V.Sc.	H	"Adult type", clean, in bundles and unaltered		Almost identical to D3
D4 <sub>5</sub> Heat Only in H <sub>2</sub> O at 37° C.	1½	40	2	—	7	None	V. few	V.V.Sc.	H	Same as starting material	No TP
	3	39	6	—	9	None	Few	V.Sc.	H	Same as starting material	No TP
	24	177	—	—	51	V.Sc.	Few	V.Sc.	VH	Same as starting material	Inc. in mod. or large pieces of L VH deposit No TP
D4 <sub>3</sub> Buffer (pH 5·0)	1½	28	1	—	10	None	V. few	V.V.Sc.	H	Same as starting material	Nearly all tiny L No TP
D4 <sub>4</sub> Periodate (pH 5·0)	1½	40	1	—	11	None	V. few	V.Sc.	H	Same as starting material	Nearly all tiny L No TP
D4 <sub>3</sub> Buffer (pH 5·0)	3	38	2	—	17	None	V. few	V.Sc.	VH	Same as starting material	Some L No TP
D4 <sub>4</sub> Buffer (pH 5·0)	3	32	—	—	10	None	V. few	V.Sc.	H	Same as starting material	Some L No TP
D4 <sub>2</sub> Buffer (pH 8·8)	24	73	1	—	10	None	V. few	V.Sc.	H	Same as starting material	Mostly L No TP
D3 51 yrs (Indigestible)											
D3 <sub>1</sub> Starting Material in H <sub>2</sub> O ..	22	—	—	3	V.Sc.	V. few	V.V.Sc.	H	"Adult type", clean, in bundles and unaltered	Nearly all L	Almost identical to D4
D3 <sub>5</sub> Heat Only in H <sub>2</sub> O at 37° C.	1½	50	—	1	25	V.V.Sc.	V. few	V.Sc.	H	Same as starting material	Nearly all L No TP
	3	64	1	—	22	V.V.Sc.	V. few	V.Sc.	H	Same as starting material	Nearly all L No TP
	24	113	—	1	18	V.V.Sc.	Few	Sc.	H	Same as starting material	Inc. in L No TP
D3 <sub>3</sub> Buffer (pH 5·0)	1½	50	5	—	8	V.Sc.	V. few	V.V.Sc.	VH	Same as starting material	Nearly all L No TP
D3 <sub>4</sub> Periodate (pH 5·0)	1½	27	1	—	13	V.V.Sc.	V. few	Sc.	VH	Same as starting material	Nearly all L No TP
D3 <sub>3</sub> Buffer (pH 5·0)	3	135	2	—	31	None	V. few	V.Sc.	VH	Same as starting material	Inc. in L No TP
D3 <sub>4</sub> Periodate (pH 5·0)	3	53	1	—	5	None	V. few	V.Sc.	H	Same as starting material	Lighter deposit No TP
D3 <sub>2</sub> Buffer (pH 8·8)	24	127	3	—	20	Sc.	V. few	Sc.	VH	Same as starting material	Nearly all L VH deposit No TP

TABLE I (continued)

## GROUP III. SUBSTRATES EXHIBITING EXCESSIVE COLLAGENASE DIGESTION

Substrate and Treatment (hrs)		Fully-Formed Elastin			TS	Fine Threads	Dense Bits	Amor-phous Material	Grid De-posit	Collagen		Elastin	Remarks
		S	F	N									
D6 20 yrs (Overdigestible)													
D6 <sub>1</sub>	Starting Material in H <sub>2</sub> O ..	65	1	—	3	Sc.	Few	Mod.	H	In clumps mixed with AM and DB. Some de-generation		Nearly all tiny pieces Only three TS	Resembled a con-trol child sub-strate
D6 <sub>5</sub>	Heat Only in H <sub>2</sub> O at 37° C.	1½	157	4	5	34	Sc.	Few	Mod.	MH	Same as starting material	Inc. in mod. large TS	No true TP
		3	138	3	6	29	Sc.	Few	Mod.	H	Same as starting material	A few large TS	No true TP
		24	136	4	4	32	Mod.	Few	Mod.	MH	More collagen starting to de-generate	A few large TS	No true TP
D6 <sub>3</sub>	Buffer (pH 5.0)	1½	Not done										
D6 <sub>4</sub>	Periodate (pH 5.0)	1½	Not done										
D6 <sub>3</sub>	Buffer (pH 5.0)	3	298	1	—	56	Sc.	Marked inc.	Marked inc.	VH	More collagen starting to de-generate	Inc. in large TS	Very marked TP
D6 <sub>4</sub>	Periodate (pH 5.0)	3	456	3	1	33	Sc.	Slight inc.	Slight inc.	H	Some starting to degenerate	Some large TS	Mod. TP
D6 <sub>2</sub>	Buffer (pH 8.8)	24	171	7	—	38	Many	Slight inc.	Slight inc.	MH	Some starting to degenerate	Some large TS	Lighter deposit Mod. TP
D7 52 yrs (Overdigestible)													
D7 <sub>1</sub>	Starting Material in H <sub>2</sub> O ..	102	—	2	12	Sc.	Few	Mod.	H	Both separate and in clumps with AM. A little degen.		Nearly all tiny pieces	Resembled a young adult con-trol substrate
D7 <sub>5</sub>	Heat Only in H <sub>2</sub> O at 37° C.	1½	119	1	1	24	None	Few	Mod.	VH	Same as starting material	Nearly all tiny pieces	No TP
		3	268	7	2	36	None	Inc.	Inc.	VH	More degen. coll.	Several large TS	No true TP
		24	82	1	2	18	Sc.	Few	Mod.	MH	More degen. coll.	Lighter deposit	No true TP
D7 <sub>3</sub>	Buffer (pH 5.0)	1½	445	5	1	51	None	Marked inc.	Marked inc.	H	Some coll. degen. S	Inc. in TS and S	Marked TP
D7 <sub>4</sub>	Periodate (pH 5.0)	1½	311	5	2	39	Sc.	Mod. inc.	Mod. inc.	H	Some coll. degen.	Inc. in TS and S	Mod. TP
D7 <sub>3</sub>	Buffer (pH 5.0)	3	265	8	1	51	V.V.Sc.	Mod. inc.	Mod. inc.	H	Some coll. degen.	Some large TS	Mod. TP
D7 <sub>4</sub>	Periodate (pH 5.0)	3	235	2	1	30	V.V.Sc.	Mod. inc.	Mod. inc.	H	Some coll. degen.		Mod. TP
D7 <sub>2</sub>	Buffer (pH 8.8)	24	252	9	2	47	Sc.	Mod. inc.	Mod. inc.	H	Some coll. degen.	Nearly all tiny pieces of S	Mod. TP

\* The N recorded were very large "networks" representing the completed conversion of the transformation structures (TS) into "Elastin". The division between some of the TS and these large "networks" was arbitrary.

L = tiny pieces of elastin presenting a stippled or lumpy appearance (as in Fig. 13).

S = skin-type elastin; F = filamenting elastin; N = natural elastin network; Num. = numerous; Mod. = moderate; TS = transformation structure; TP = transformation picture; DB = dense bits; AM = amorphous material; H = heavy; VH = very heavy; MH = moderately heavy; V.Sc. = very scanty; degen. = degenerating; Inc. = increased.

Total "elastin" counts { from the two substrates in Group III = 4,124 }  
 { from the six substrates in Group II = 4,006 } 21,576  
 { from the five substrates in Group I = 13,446 }



Substrate and Treatment (hrs)	Group I Average Collagenase Digestion							Fully-Formed Elastin		
	Fully-Formed Elastin			TS	Grid Deposit	"Elastin" Increase	Transformation Picture	S	F	N
	S	F	N							
Starting Material Heat only in H <sub>2</sub> O at 37° C.	1½ 2-3 24	D12 20 mths 2-3 5 12	— — —	— — 7	H H VH	Unexpected picture. VH deposit	Marked	D8 19 mths Not done 1-1½ 1-1½	— — —	— — —
Buffer (pH 5.0)	3	6	—	21	MH	Sig. inc. S, N, and TS	Marked	2-3	—	—
Periodate (pH 5.0)	3	8	—	13	H	Sig. inc. S, N, and TS	Marked	—	—	—
Buffer (pH 8.8)	24	5-6	1½	—	H	No inc. over unexpected 24-hr heat-only picture.	Mod.	—	—	—
Starting Material Heat only in H <sub>2</sub> O at 37° C.	1½ 3 24							D11 5½ yrs Not done 1½ 2	— — —	— — —
Buffer (pH 5.0)	3							—	—	—
Periodate (pH 5.0)	3							1½	—	—
Buffer (pH 8.8)	24							2-3	—	—
Starting Material Heat only in H <sub>2</sub> O at 37° C.	1½ 3 24	D13 9 yrs 1-2 2 2	2 — —	— — —	H H H			D9 9½ yrs Not done 2	— — —	— — —
Buffer (pH 5.0)	3	5-6	—	3	3-4	Sig. inc. S, N, and TS	Marked	2-3	—	—
Periodate (pH 5.0)	3	5-6	2	—	2	Sig. inc. S and TS	Mod.	—	—	—
Buffer (pH 8.8)	24	4	5	3	3-4	Sig. inc. S, F, N, and TS	Mod.	1-2	—	—
Starting Material Heat only in H <sub>2</sub> O at 37° C.	1½ 3 24							D10 13 yrs 2 — — 3	— — — —	— — — —
Buffer (pH 5.0)	3							—	—	—
Periodate (pH 5.0)	3							—	—	—
Buffer (pH 8.8)	24							—	—	—
Starting Material Heat only in H <sub>2</sub> O at 37° C.	1½ 3 24	D14 19 yrs — — —	— — —	— — —	H H H	Unusually high counts		D4 18 yrs 2 2 8	— — —	— — —
Buffer (pH 5.0)	1½	Not done	—	—	H			2	—	—
Periodate (pH 5.0)	1½	Not done	—	—	H			2	—	—
Buffer (pH 5.0)	3	1-2	—	—	H	Slight inc. S and TS	Marked	2	—	—
Periodate (pH 5.0)	3	1-2	—	—	H	Slight inc. S and TS	Mod.	1-2	—	—
Buffer (pH 8.8)	24	1-2	—	—	H	Slight inc. S and TS	Mod.	3-4	—	—
Starting Material Heat only in H <sub>2</sub> O at 37° C.	1½ 3 24	D5 43 yrs 2-3 5 1-2	— — —	— — —	VH VH VH					
Buffer (pH 5.0)	1½	3-4	—	—	H	Mod. inc. S and TS (H deposit)	Mod.			
Periodate (pH 5.0)	1½	3-4	—	—	H	Mod. inc. S and TS (H deposit)	Mod.			
Buffer (pH 5.0)	3	6	—	—	H	Mod. inc. S and TS (H deposit)	Mod.			
Periodate (pH 5.0)	3	1-2	—	—	H	No sig. inc. (unexpected picture)	—			
Buffer (pH 8.8)	24	5	—	—	VH	Mod. inc. S and TS (VH deposit)	Mod.			
Starting Material Heat only in H <sub>2</sub> O at 37° C.	1½ 3 24	D15 56 yrs — 1-2 1-2	— — —	— — —	H H H			D3 51 yrs 2 3 5 3	— — — —	— — — —
Buffer (pH 5.0)	1½	Not done	—	—	H			—	—	—
Periodate (pH 5.0)	1½	Not done	—	—	H			—	—	—
Buffer (pH 5.0)	3	2-3	—	—	H	Slight inc. small pieces S	None	6	—	—
Periodate (pH 5.0)	3	2-3	—	—	H	Slight inc. small pieces S	None	2-3	—	—
Buffer (pH 8.8)	24	2-3	—	—	H	Slight inc. small pieces S	None	5-6	—	—

Figures represent number of times "elastin" content increased over that present in starting material.

S = Skin-type elastin.

F = Filamenting elastin.

N = Natural elastin network.

TS = Transformation structure.

Mod. = Moderate.

COUNTS FROM ALL GROUPS

Group II Collagenase-Resistant				Group III Excessive Collagenase Digestion						
TS	Grid Deposit	"Elastin" Increase	Trans- formation Picture	Fully-Formed Elastin			TS	Grid Deposit	"Elastin" Increase	Trans- formation Picture
				S	F	N				
3 2-3	H MH MH									
10 2 2	H MH MH	Sig. inc. S and TS No sig. inc. No sig. inc.	Marked None None							
2 2 — — 2	H H H H VH	No sig. inc. No sig. inc. No sig. inc.	None None None							
2 1-3 4 1-2 1-2	H H MH H MH MH	Sig. inc. TS No sig. inc. (MH deposit) No sig. inc. (MH deposit)	Mod. None None							
1-2 1-2 1-2 1-2 2	H H H H MH H	No sig. inc. No sig. inc. V. slight inc. S	None None None							
— — 1-4 — — — — —	H H H VH H H VH H H	No sig. inc. No sig. inc. No sig. inc. No sig. inc.	None None None None	D6 20 yrs 2-3 — 2 — 2 — Not done Not done 4-5 — 7 — 2-3 —	— — — — — — — — —	— — — — — — — — —	11 9 10 18 11 12	H MH H MH VH H MH	Sig. inc. S and TS Sig. inc. S and TS Mod. inc. S and TS	V. marked Mod. Mod.
8 7 6 2 4 10 — 6	H H H H VH VH VH H VH	No sig. inc. (VH deposit) No sig. inc. (VH deposit) Slight inc. only (VH deposit) No sig. inc. No sig. inc.	None None None None None	D7 52 yrs — — — 2-3 — — — — — — 4-5 — — — 3 — — — 2-3 — — — 2-3 — — — 2-3 — — —	— — — — — — — — —	— — — — — — — — —	2 3 — 4 3 4 2-3 4	H VH VH MH H H H H H	Sig. inc. S and TS Sig. inc. S and TS Sl. inc. S and TS (H deposit) Sl. inc. S and TS (H deposit) Mod. inc. S and TS (H deposit)	Marked Mod. Mod. Mod. Mod.

"Elastin" increase column estimated by subtracting relevant heat-only increase and allowing for variations in density of grid deposit.

Sl. = Slight.  
H = Heavy.  
VH = Very heavy.  
MH = Moderately heavy.  
Sig. inc. = Significant increase.

TABLE III  
SUMMARIZED ELECTRON MICROSCOPIC CHARACTERISTICS OF THE THREE GROUPS

Group	I Average Collagenase Digestion	II Collagenase- Resistant	III Excessive Collagenase Digestion
Starting Material	Usual age differences In young subjects collagen often in clumps with abundant amorphous material and dense bits In older subjects cleaner collagen in bundles with less amorphous material and dense bits Elastin tended to increase with age	Very little age difference All very similar, consisting of bundles of clean collagen and hardly any amorphous material and dense bits Elastin tended to decrease with age	Resembled Group I specimens from younger age groups; e.g. 20-yr-old was similar to substrate from a child control
Elastin		Much scantier than Groups I and III after all treatments High proportion of L* Many small bundles of collagen resembling elastin (Fig. 9)	
Response to Heating in H <sub>2</sub> O up to 24 hrs at 37° C.	Slight increase in skin-type "elastin" No transformation picture	Slight increase in skin-type "elastin" and transformation structures No transformation picture	Slight increase in skin-type "elastin" and transformation structures No transformation picture
Response to Borate Buffer (pH 8.8) 24 hrs at 37° C.	Moderate transformation picture in children and young adults Increase in amorphous material and dense bits	No effect except slight increase in amorphous material and dense bits	Moderate transformation picture equal to younger control subjects
Response to Phthalate Buffer (pH 5.0) 3 hrs at 37° C.	Marked transformation picture under 20 yrs, moderate in 43-yr-old, and absent in 56-yr-old	Marked transformation picture in infant and moderate in 9½-yr-old Otherwise no effect	Transformation picture very marked in 20-yr-old and marked in 52-yr-old
Response to Periodate in Phthalate Buffer (pH 5.0) 3 hrs at 37° C.	Less effect in same substrates as responded to phthalate buffer alone	No effect	Less effect than to phthalate buffer alone, giving moderate transformation picture

\* L = tiny pieces of elastin presenting a stippled or lumpy appearance as illustrated in Fig. 13.

were seen throughout all the experiments performed on this particular substrate.

A totally different picture was found in the group that did *not* digest after incubation with collagenase (Group II). The starting materials were very similar to each other (Figs 2, 3, 4, and 7). Even the substrate from the infant (D8, Fig. 2) closely resembled that found in the adults, with bundles of clean, unaltered collagen fibrils. There was also a notable absence of amorphous material and dense bits, which caused small bundles of collagen to resemble filamenting elastin on the electron microscopic viewing screen. Continual examination through the magnifying eyepiece was necessary to get a correct "elastin" count throughout this group (Fig. 9).

The two substrates exhibiting excessive collagenase digestion (Group III) resembled younger specimens of the control group: the 20-year-old (D6, dead of fulminating acute rheumatic carditis) could be mistaken for a child's dermis, and the 52-year-old (D7, who had received intravenous nitrogen mustard 4 days before death as therapy for

carcinoma of the lung) resembled the dermis of a young adult.

In all three groups, the majority of the "elastin" counted was in tiny pieces, and frequently presented a stippled or lumpy appearance in Group II (Fig. 13a-c). As already mentioned, occasional large, dense, square-ended fibres, similar to those found in untreated, fresh whole dermis (Keech and Reed, 1957) were seen in all the prepared substrates used in the present study (Figs 10-12). The transformation structures (TS), described above and present in all the prepared starting materials, appear to be an altered form of these naturally-occurring dermal components.

In Groups I and III the elastin content of the starting material showed a tendency to increase with age: an exception was the unexpectedly high count in the 19-year-old substrate (D14). In Group II not only was the elastin scanty but the trend appeared to be in the reverse direction.

*Treatment in H<sub>2</sub>O at 37° C.*—Table I shows that heat alone produced a progressive increase in

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The scale marked on all the figures represents  $1\mu$  and all the preparations were shadowed with chromium

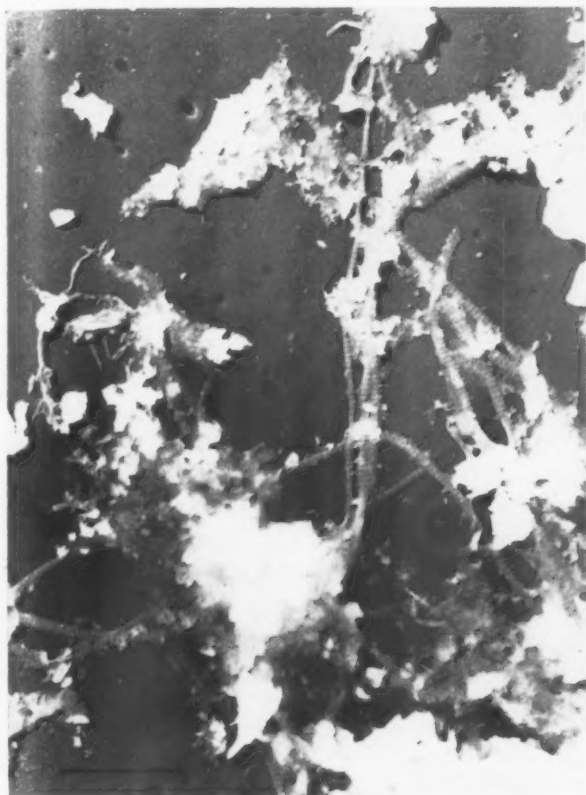


Fig. 1.—Prepared abdominal skin collagen from an infant aged 20 months (Control group D12). This starting material shows the striated collagen fibrils mixed with, and partially obscured by, the plentiful amorphous material and dense bits.

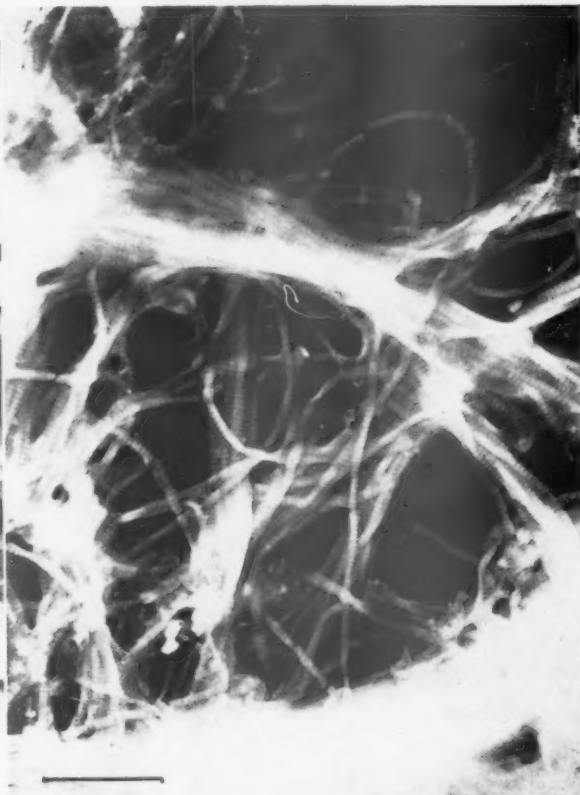


Fig. 2.—Starting material from an infant aged 19 months (Collagenase-resistant group D8). In contrast to Fig. 1 the substrate consists of bundles of clean collagen fibrils with a notable absence of amorphous material and dense bits.

skin-type "elastin" counts in all groups, directly proportional to the length of incubation. This effect, therefore, must be taken into account when assessing the action of any chemical treatment. Group II reacted least, whereas Group III and the youngest member of Group I gave the greatest reactions. In fact, the 24-hr picture in D12<sub>s</sub> was unexpected and gave a much higher count than any other treatment, aided by a very heavy grid deposit. Another substrate (the 20-year-old D6 from Group III that resembled a control child dermis) reacted in a similar fashion, together with a marked increase in TS, in spite of only moderately heavy grid deposits. Apart from those just mentioned, the majority of the substrates showed an increase in skin-type "elastin" two or three times greater than that present in the starting material (Table II), this increase consisting almost entirely of tiny or moderately-sized pieces and *not* constituting a transformation picture as defined above.

N (Fig. 14), mentioned in the elastin columns of Table I, denotes the medium-sized, compact structures previously described (Keech, Reed, and Wood, 1956). However, heat alone on the substrates from both the infants (D12 and D8) produced large networks, sometimes stretching over several microscopic fields ( $20-30\mu$  in length), and composed of loosely-knit, winding bundles of filamenting "elastin" (Fig. 15). This was much more marked in D12 than D8.

*Effect of Phthalate Buffer (pH 5.0) Alone at 37° C.* (Tables I and II).—3-hr incubation samples were examined throughout all groups, but only four substrates were examined at  $1\frac{1}{2}$  hrs, as it was found that a better response occurred with longer incubation. A significant increase (above that which could be accounted for by heat alone) was found in both skin-type and TS throughout Groups I and III, and in two of the younger subjects gave the





Fig. 3.—Starting material from an individual aged 18 years (Collagenase-resistant group D4). Again the substrate is typical of Group II. Compare with Figs 2, 4, and 7.

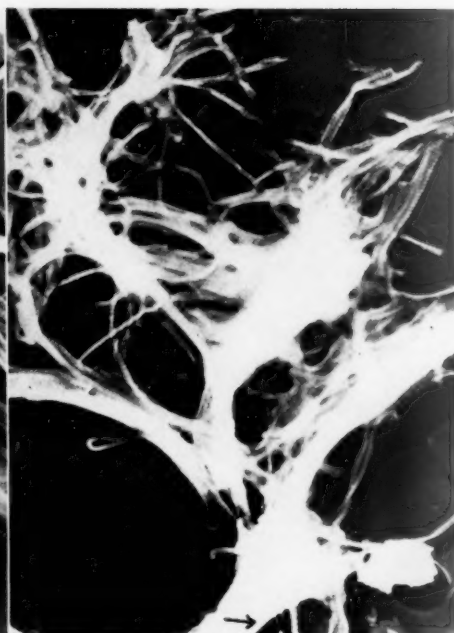


Fig. 4.—Starting material from a 13-year-old substrate (Collagenase-resistant group D10). This is again typical of Group II. The arrow indicates part of a collagen fibril under tension, as illustrated and described previously (Keech and others, 1956).



Fig. 5.—Starting material from an individual aged 19 years (Control group D14). The collagen is mixed with a moderate amount of amorphous material and dense bits.

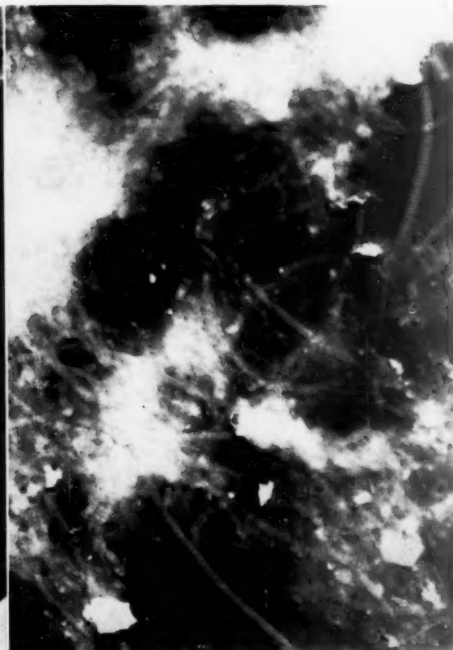


Fig. 6.—Starting material from a 20-year-old substrate (Group exhibiting excessive collagenase digestion D6). Compared with the control of the same age (Fig. 5), a fair number of the collagen fibrils are starting to degenerate, and the general picture on the electron microscopic viewing screen resembled younger specimens from the control group.



Fig. 7.—Starting material from an individual aged 51 years (Collagenase-resistant group D3), showing the substrate typical of this group. Compare with Fig. 8.

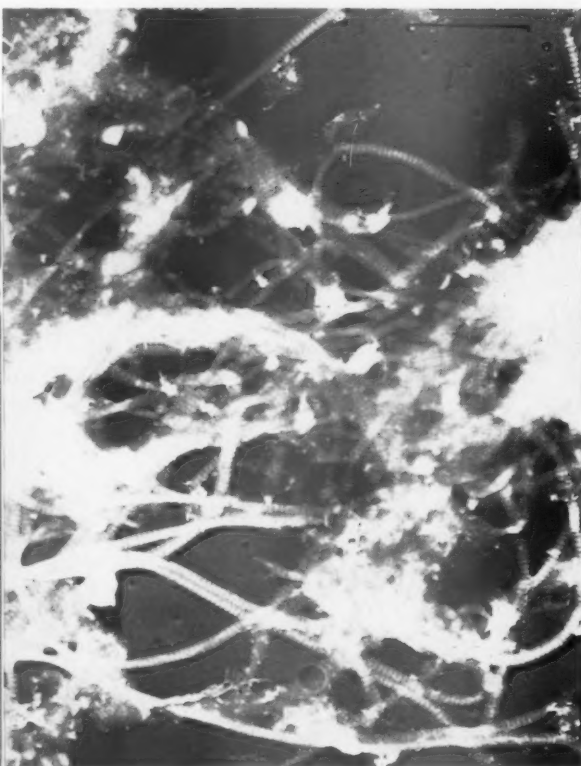


Fig. 8.—Starting material from a 56-year-old adult (Control group). The collagen is mixed with a small amount of amorphous material and a few dense bits. Compare with Fig. 7.

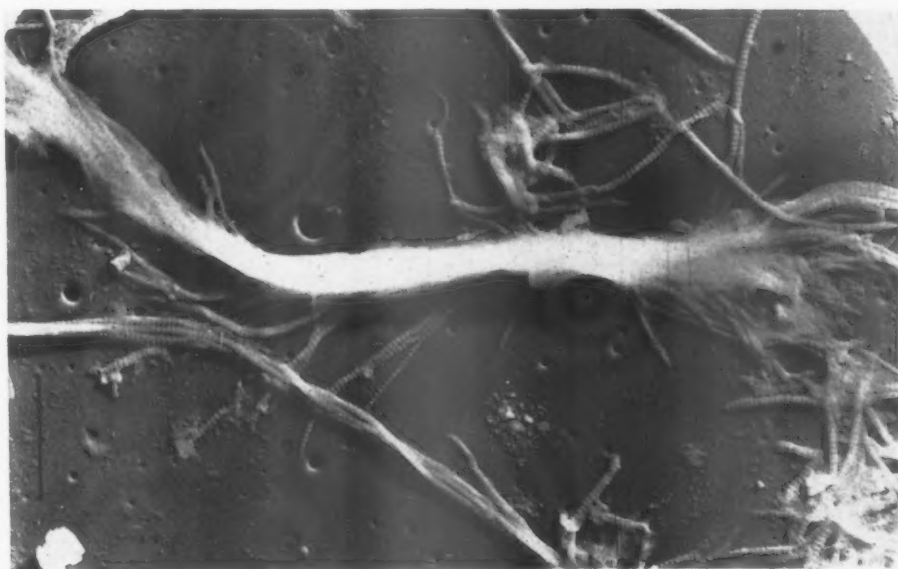
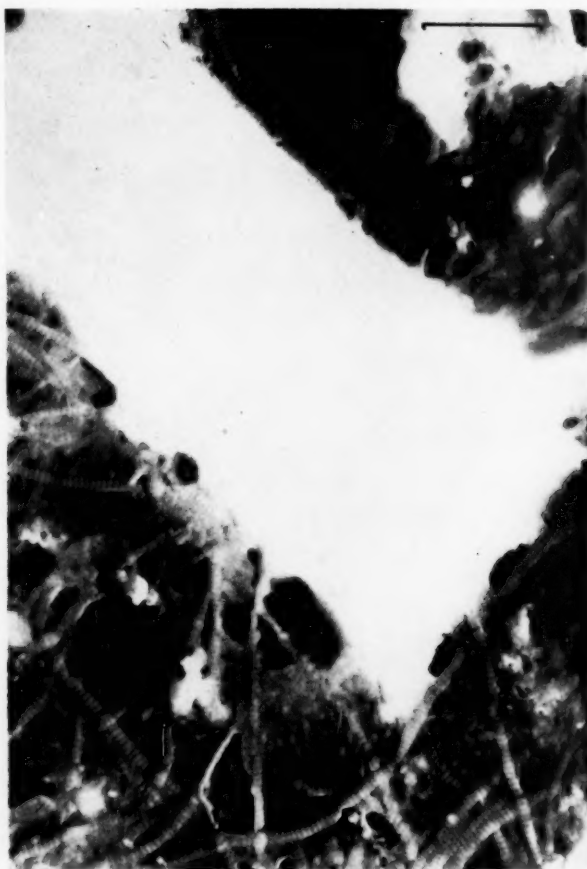


Fig. 9.—Two examples of bundles of collagen, partially coated with a thin layer of amorphous material which resembled filamenting elastin on the electron microscopic viewing screen. These were characteristic of Group II.



Figs 10 and 11.—Examples of square-ended, large, dense fibres from the fresh whole dermis of a 66-year-old adult. These were seen in both fresh and prepared dermis from all age groups, and sometimes splayed out into a bundle of collagen fibrils.



Fig. 12.—Starting material from a 9½-year-old child (Collagenase-resistant group D9), showing a branched example of the large dense fibres illustrated in Figs 10 and 11.

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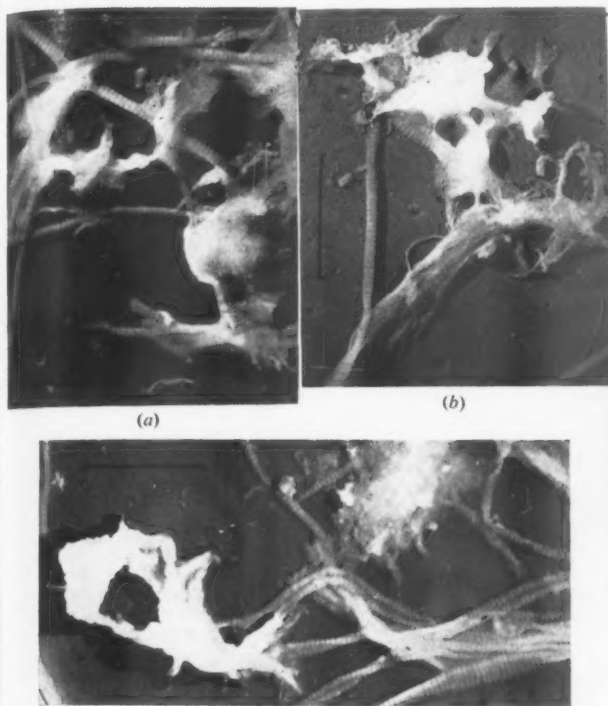


Fig. 13(a), (b), (c).—Examples of tiny pieces of elastin presenting a stippled or lumpy appearance which characterize Group II.

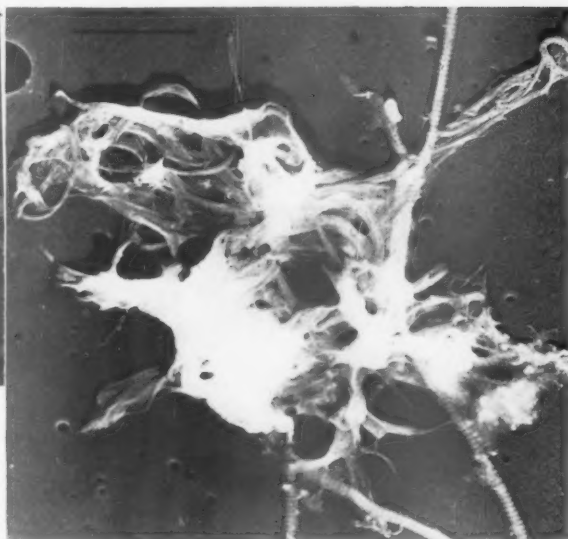


Fig. 14.—A typical compact, ordinary network from the starting material of the 56-year-old adult (Control group D15). This is one variant of the naturally occurring or fully-formed elastin described previously (Keech and others, 1956).

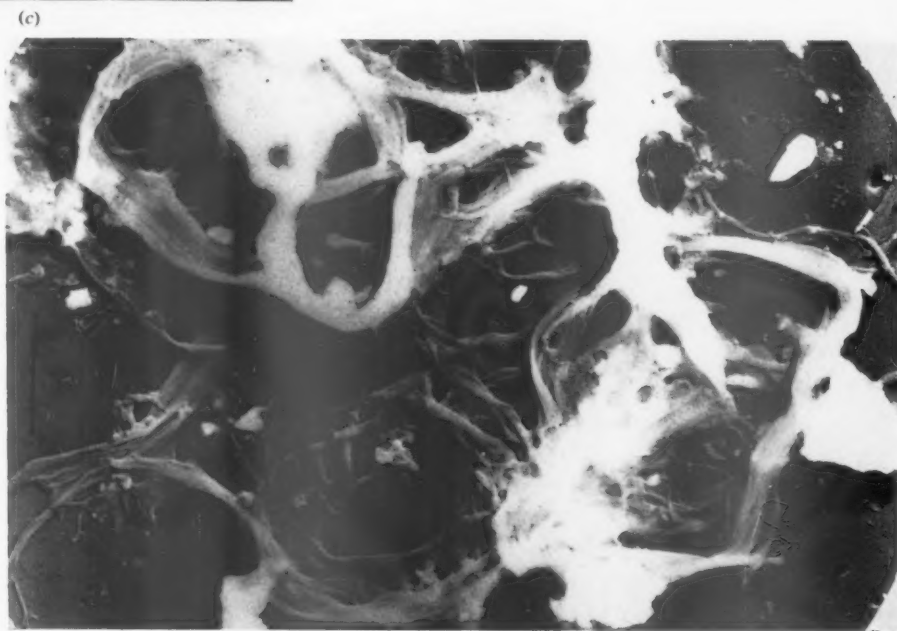


Fig. 15.—In contrast to Fig. 14, when the substrates from both the infants (D12 and D8) were heated in water at 37° C., large networks were produced, sometimes stretching over several microscopic fields. These networks measured 20-30 $\mu$  in length, and were composed of loosely-knit, winding bundles of filamentous "elastin".

highest readings, *e.g.* D12 and D13, in which the network counts were also significantly raised. In contrast, the 56-year-old control exhibited a slight increase in small pieces of skin-type only, and the

majority of Group II were unresponsive. In the substrates which responded, a marked transformation picture was produced in the younger subjects (Fig. 37) and in Group III, but only a moderate



transformation occurred in the 43-year-old adult control and the 9½-year-old indigestible.

*Effect of Periodate in Phthalate Buffer (pH 5.0) at 37° C. (Tables I and II).—*Samples were examined after the same periods of incubation as were used

in the experiment with buffer alone. A definite, but less marked, response was found in all the substrates in Groups I and III that reacted to buffer alone to give a moderate transformation picture (Figs 16 and 17), but *no* effect was produced in the group resistant to collagenase.

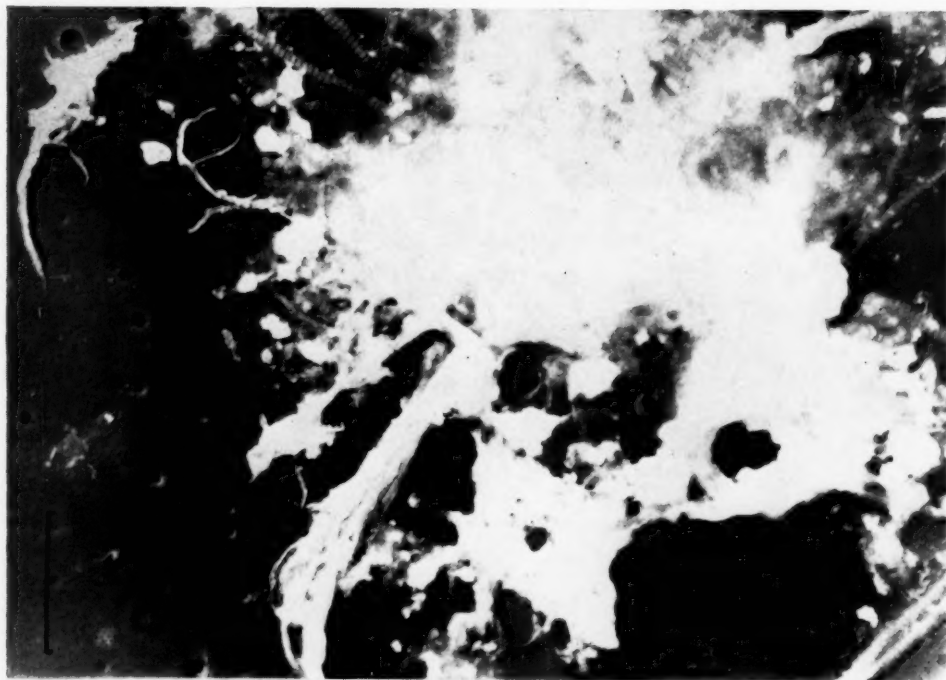


Fig. 16.—Effect of phthalate buffer (pH 5.0) alone on the 19-year-old substrate (D14) from the Control group. After 3 hrs' incubation at 37° C., a transformation picture was found, with a significant increase in the "elastin" counts. This shows degenerating collagen mixed with amorphous material and elastin-like structures. Compare with Fig. 17.

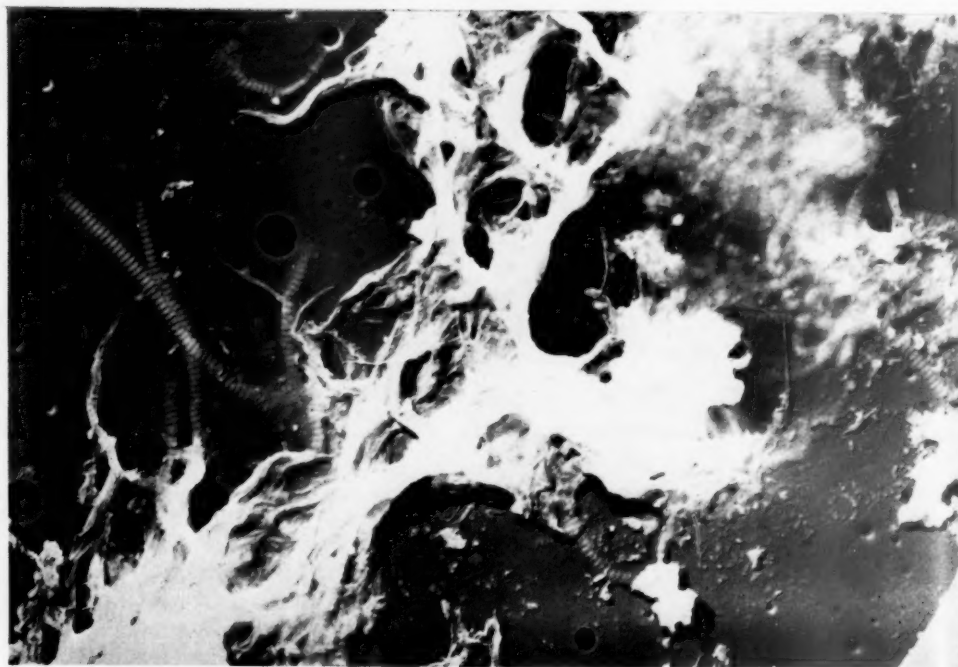


Fig. 17.—Effect of periodate in phthalate buffer (pH 5.0) on the 20-year-old substrate exhibiting excessive collagenase digestion (D6). A transformation picture was found after 3 hrs' incubation at 37° C. with collagen (some of which was starting to degenerate) mixed with amorphous material and elastin-like structures. Compare with Fig. 16.

*Effect of Borate Buffer (pH 8.8) for 24 hrs at 37° C.* (Tables I and II; Figs 18-25).—The usual increase in amorphous material and dense bits was found in all substrates, being most marked in Groups I and III. A significant increase in "elastin" counts was seen in all the control substrates (with the exception of D12 owing to the gross increase after heat alone for 24 hrs), being of moderate degree and accompanied by a moderate transformation picture. However, in the 56-year-old adult, there was a slight increase in skin-type only and no transformation picture. Both the 20- and 52-year-old substrates in Group III gave a moderate increase in skin-type and TS with a moderate transformation picture. In contrast, none of Group II had "elastin" counts significantly raised above that which could be accounted for by heat alone. The markedly different responses to alkali by substrates of the same age but belonging to different groups, is illustrated in Figs 18-25.

#### Collagen (Table I)

The variation in the starting materials has already been described (Figs 1-8). In general, the younger the substrate, the more easily could fairly mild agents induce fibril degeneration, whereas the older substrates remained relatively unaltered. For

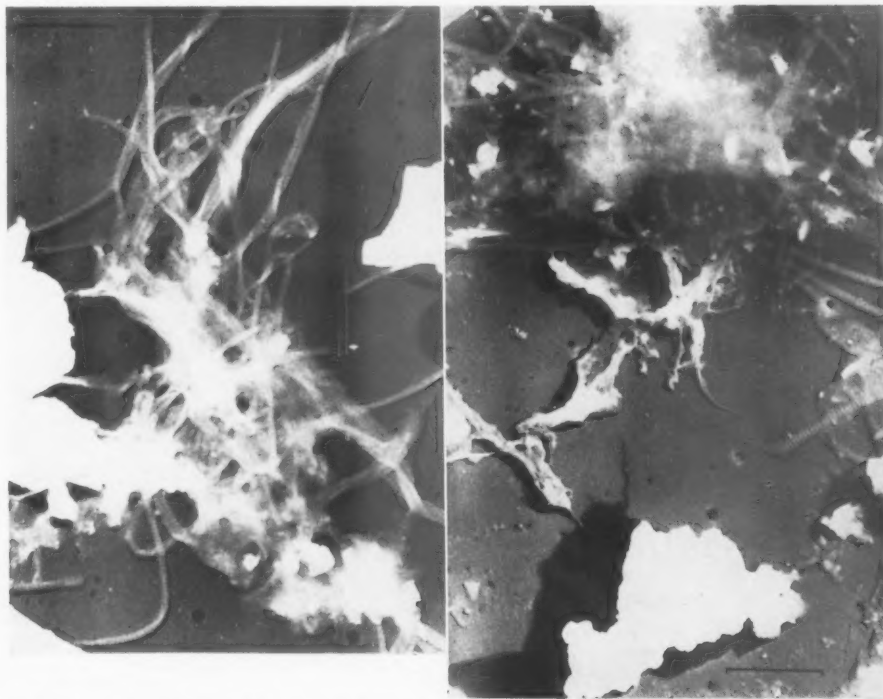
example, heat alone for 24 hrs caused a small proportion of the infant collagen D12 to exhibit the early stages of degeneration, and the only substrate in Group II to show any collagen alteration after any treatment was the infant D8. The liability of fibril degeneration also varied between the three groups, being most marked in Group III and nearly absent in Group II.

#### Elastin

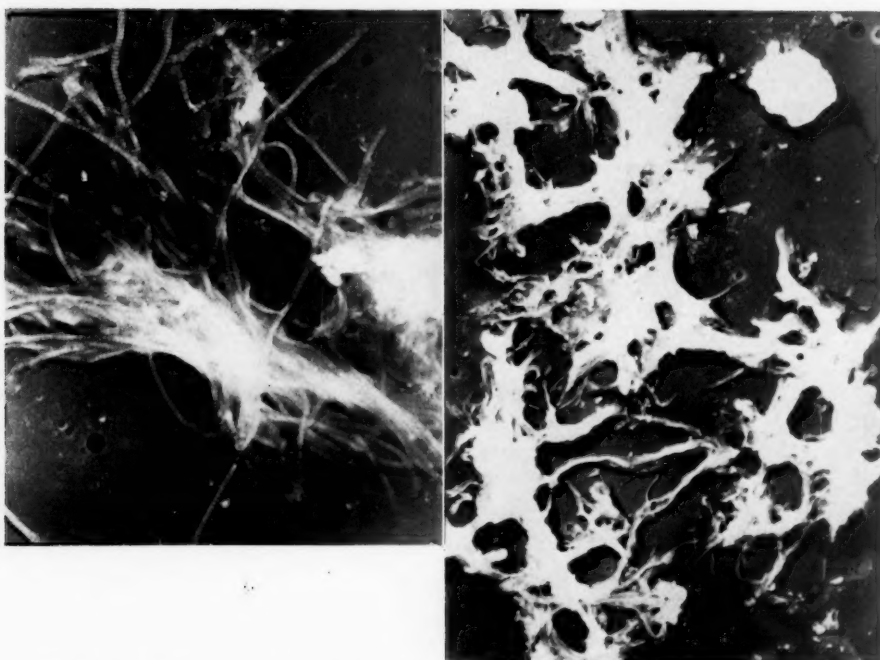
The different variants have been described above under "Terminology", and the effect of treatment is shown in Table I. The examples of the so-called transformation structures illustrated in Figs 26-35 underline the wide range of variants seen, and Figs 36 and 37 show small areas of the almost continuous transformation picture found in the substrate from the infant (D12) after treatment either with phthalate buffer alone or with periodate in buffer.

#### Amorphous Material and Dense Bits

These were plentiful in the younger subjects of Group I and scarcer in the adults. They were strikingly absent in Group II. Incubation with alkaline buffer produced an increase in all substrates, being least noticeable in Group II.



Figs 18 and 19.—Effect of incubation in borate buffer (pH 8.8) for 24 hrs at 37° C. The collagenase-resistant substrate from the infant (D8) illustrated in Fig. 18 was practically unaltered, whereas the control substrate from the infant (D12) illustrated in Fig. 19 produced a transformation picture. There was an increase in amorphous material and dense bits in both, but this was less marked in D8.



Figs 20 and 21.—Effect of incubation in borate buffer (pH 8.8) for 24 hrs at 37° C. The 9½-year-old collagenase-resistant substrate (D9) remained unaltered (Fig. 20), whereas the 9-year-old control (D13) produced a transformation picture. Fig. 21 illustrates part of a sheet of "elastin networks".

### Fine Thread-like Structures

These were described by Keech and others, 1956. They were only found in very small numbers throughout this study, being virtually absent in Group II. Alkaline buffer produced an increase in most of the substrates in Groups I and III.

### Manufactured Networks (MN)

Small and medium-sized structures closely resembling the MN described previously (Keech and others, 1956) were occasionally seen throughout the present study. They numbered one to twenty for each substrate (*i.e.* per 8-11,000 fields), and there was no correlation with either age, treatment, or "elastin" increase. However, though present throughout Groups I and III, they were only found in two of the youngest substrates in Group II.

### Discussion

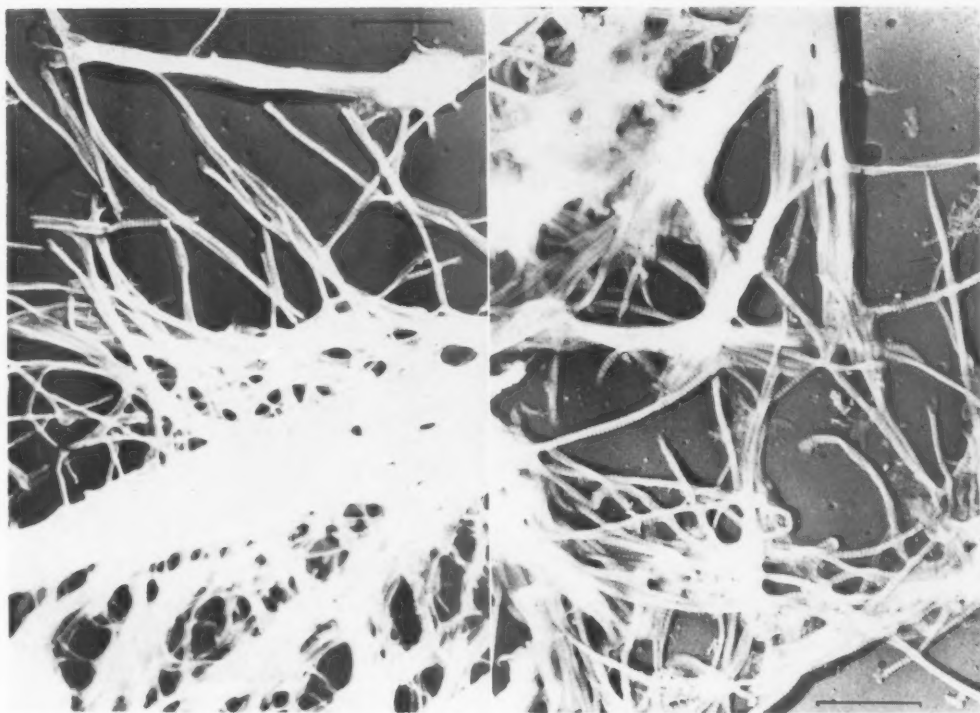
Several points arise out of the electron microscope part of this study (Table III):

(1) Treatment of the substrates in water at 37° C. could produce an increase of up to two or three times the amount of skin-type "elastin" at 24 hrs (Tables I and II). This was associated with relatively unaltered collagen fibrils and did *not* con-

stitute a transformation picture (the exception of D12 has already been mentioned). This finding confirms previous work (Keech and Reed, 1957) on fresh whole dermis, where such an increase was found in all age groups after prolonged incubation, in either water or normal saline, at or below body temperature. This increase was allowed for in estimating the effects of the various reagents, as explained in Table II. However, there was a group difference, Group II showing the least and Group III the greatest responses.

(2) The response to treatment with all the reagents used was dependent on age. The decrease in collagen breakdown as age increased paralleled the quantitative increase in "elastin" recorded in Groups I and III. This lessening reactivity to chemical agents with advancing years is reminiscent of the similar response obtained from identical substrates after incubation with collagenase (Keech, 1954a). However, Group II did not react to either collagenase or to alkali, suggesting that the enzyme may attack similar linkages within the collagen molecule.

(3) This age-dependent response was associated with an age-difference in the collagen fibrils themselves, both in the starting materials within the



Figs 22 and 23 show the unaltered appearances of the 13-year-old (D10) and 18-year-old (D4) collagenase-resistant substrates respectively.

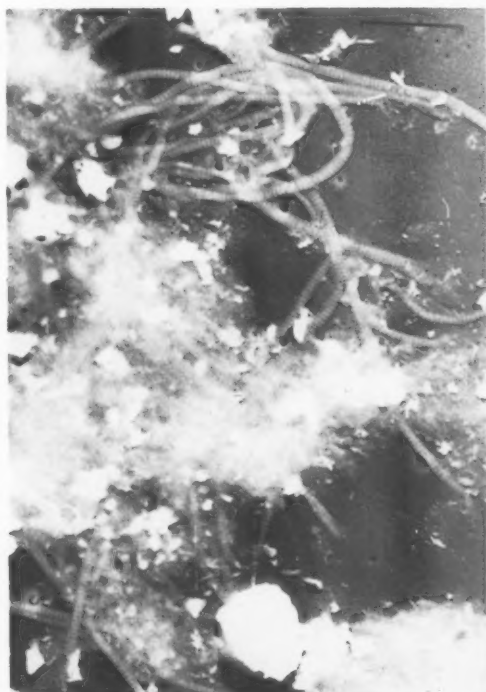


Fig. 24 demonstrates the degenerate appearance of the 19-year-old control collagen (D14) with an increase in amorphous material and dense bits.



Fig. 25 illustrates part of one of the many large transformation structures found in the 20-year-old substrate exhibiting excessive collagenase digestion (D6).

Figs 22 to 25.—Effect of incubation in borate buffer (pH 8.8) for 24 hrs at 37° C.





Fig. 26.—Transformation structure (TS) from the 51-year-old collagenase-resistant substrate (D3) after heating in water for 24 hrs at 37° C. The two arrows indicate a striated collagen fibril which apparently changes to "elastin". The single arrow demonstrates part of a collagen fibril under tension, as illustrated and described previously (Keech and others, 1956).



Fig. 27.—Transformation structure (TS) from the 52-year-old substrate exhibiting excessive collagenase digestion (D7), after incubation in phthalate buffer (pH 5.0) for 1½ hrs at 37° C. The thick, elastin-like structure splays out into a bundle of collagen fibrils at the upper left corner of the picture. The arrow indicates part of a collagen fibril under tension and raised above the surface of the grid as demonstrated by the direction of the shadow (Keech and others, 1956).

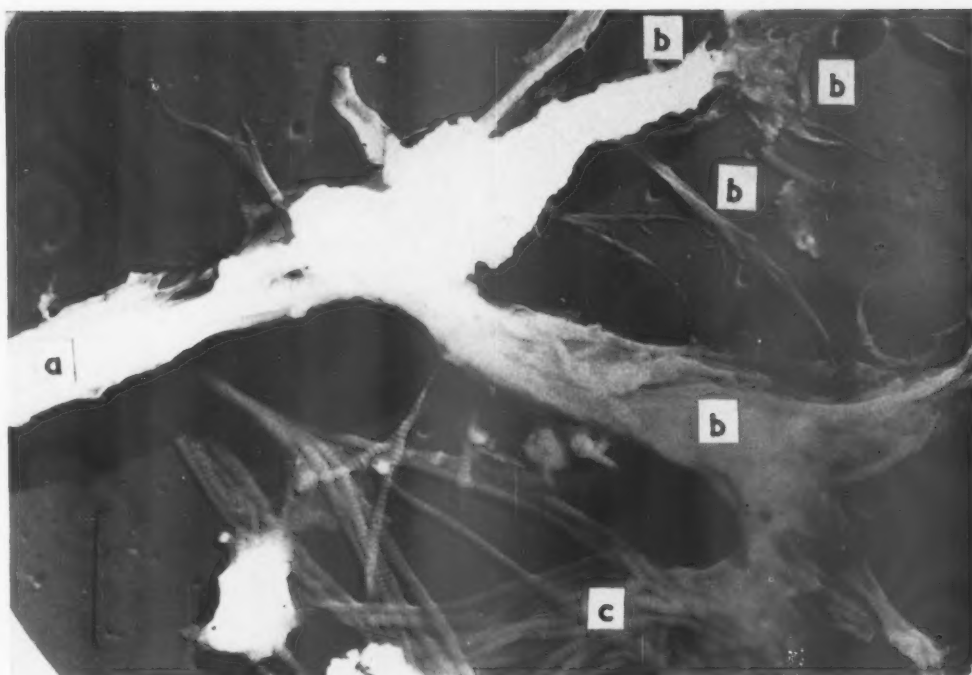


Fig. 28.—Transformation structure (TS) from the 5-year-old collagenase-resistant substrate (D11) after heating in water for 24 hrs at 37° C. The dense bundle (a) splays out into several areas typical of "elastin" (b-b) finally merging into a bundle of collagen fibrils (c).

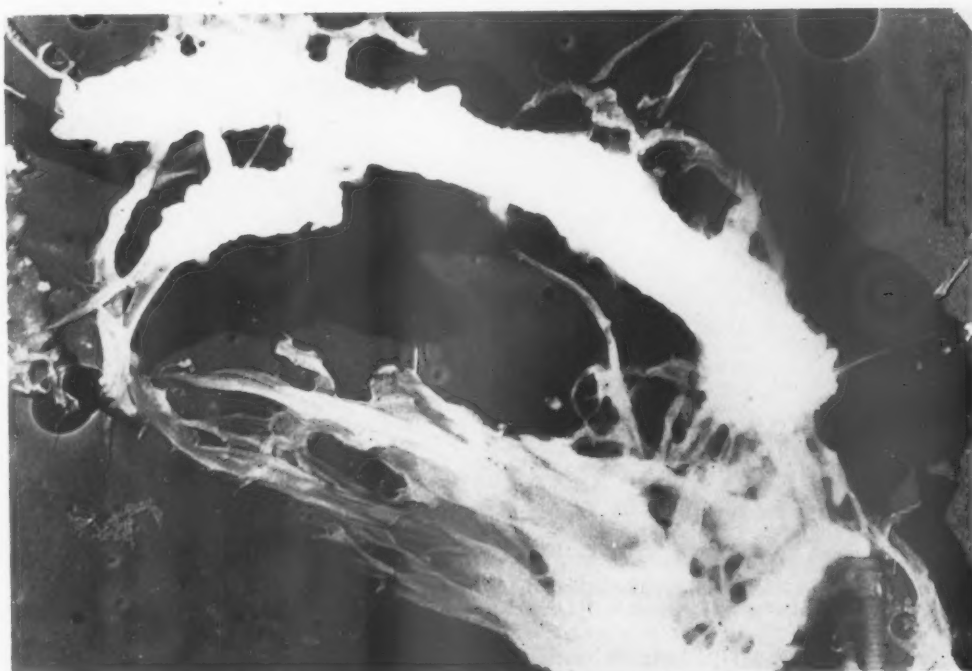


Fig. 29.—Transformation structure (TS) from the 19-year-old control starting material (D14). Each end of the dense bundle splays out into elastin-like material.

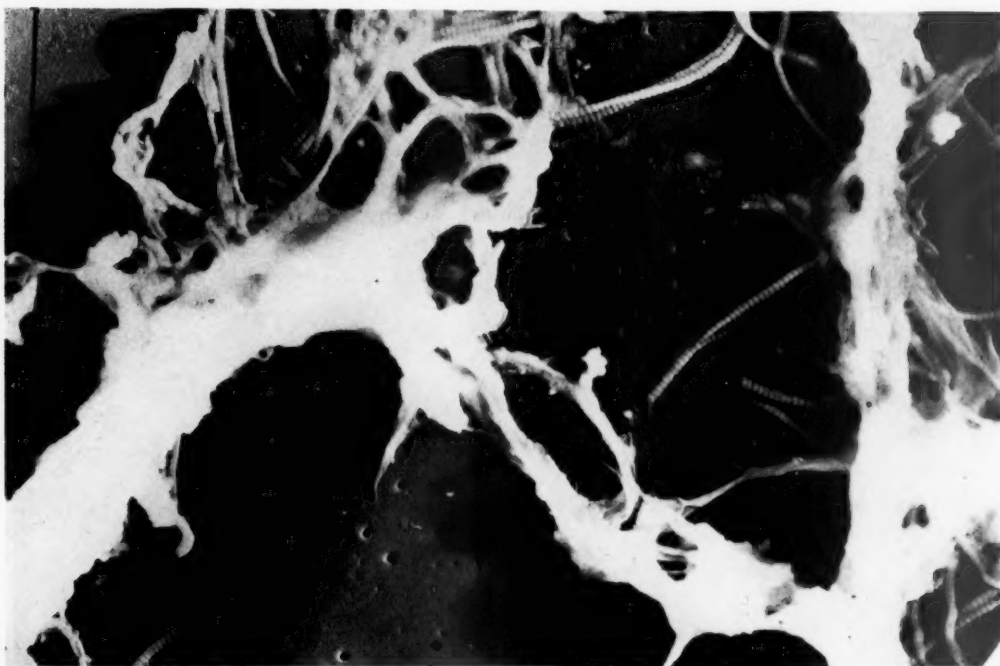


Fig. 30.—Part of a large transformation structure (TS) from the 51-year-old collagenase-resistant substrate (D3) after incubation with periodate in phthalate buffer (pH 5.0) for 1½ hrs at 37° C. The elastin-like material is intimately associated with the striated collagen fibrils.

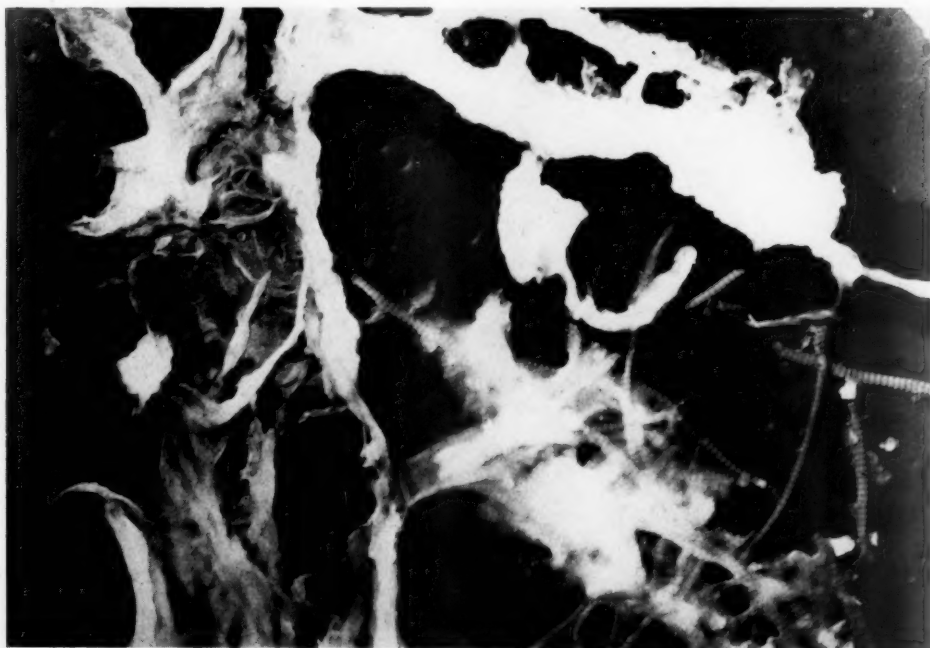


Fig. 31.—Part of a large transformation structure (TS) from the 9½-year-old collagenase-resistant substrate (D9) after heating in water for 24 hrs at 37° C. Each end of the dense bundle splays out into "elastin".

control group and *between* groups (see Table III). The appearance of the fibrils reflected the *reactivity* of each particular substrate: when they showed

evidence of degeneration, the "elastin" counts were increased and transformation pictures were found. On the other hand, the *unaltered* fibrils in Group II

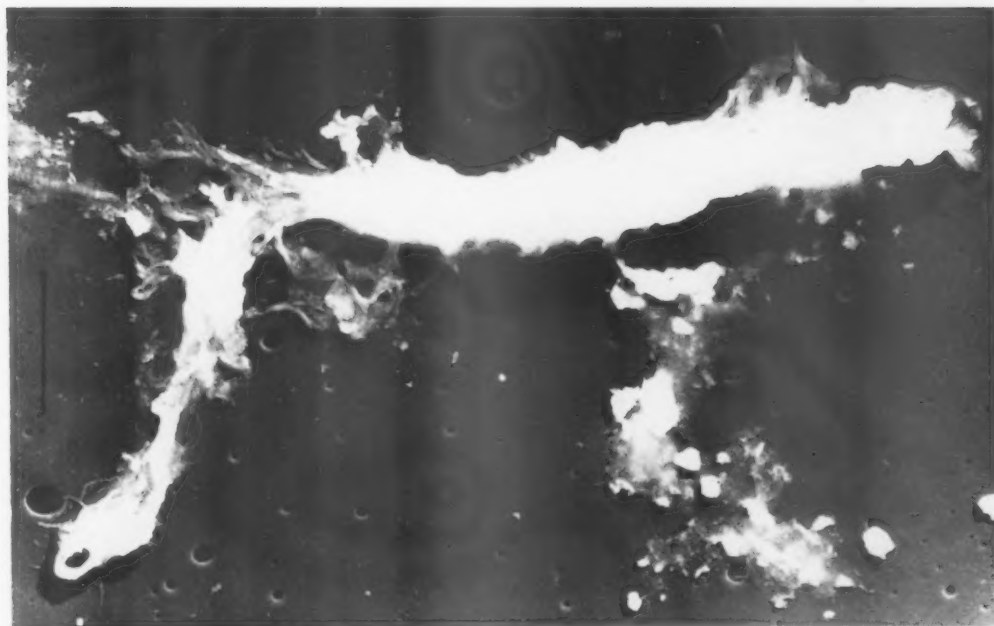


Fig. 32.—A small transformation structure (TS) from the 9-year-old control substrate (D13) after heating in water for 1½ hrs at 37° C. The smaller quantity of electron-opaque material at one end allows the underlying elastin-like nature of the structure to be revealed.

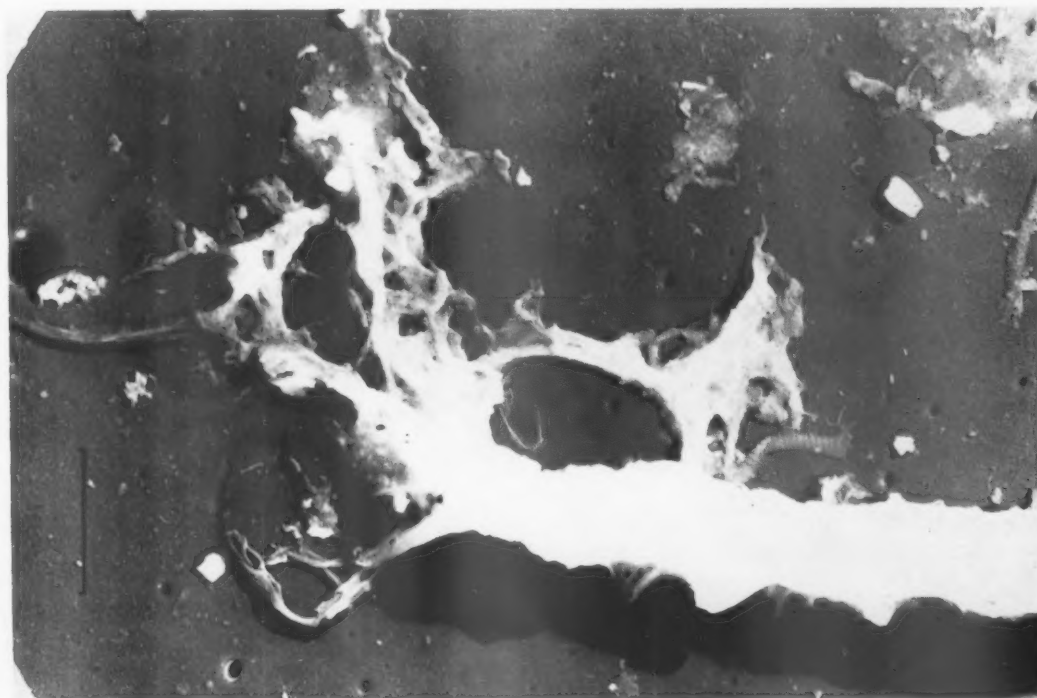


Fig. 33.—Transformation structure (TS) from the same substrate as Fig. 32 after incubation in phthalate buffer (pH 5.0) for 3 hrs at 37° C. Part of a long, dense bundle terminating as "elastin".

correlated with the lack of response which characterized this particular group.

(4) The same reagents had different effects on

different groups. The response of the three groups showed a striking similarity to their known reactivity towards collagenase: the collagenase-resistant sub-



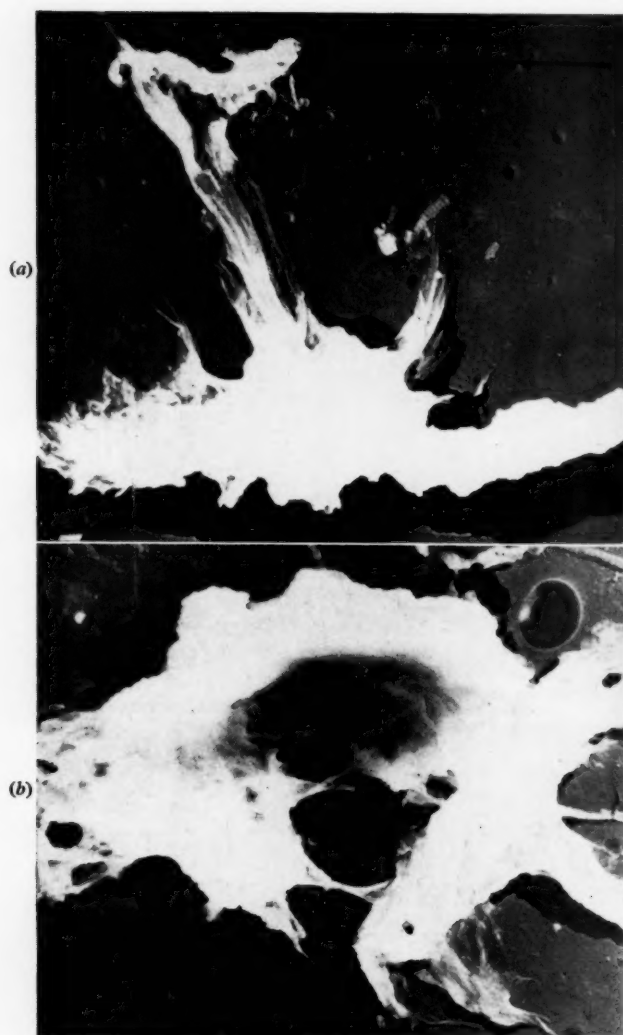


Fig. 34(a, b).—Two small transformation structures (TS) demonstrating the appearance of elastin-like material where the dense coating of amorphous material is reduced in amount. Numerous examples were seen throughout this investigation.

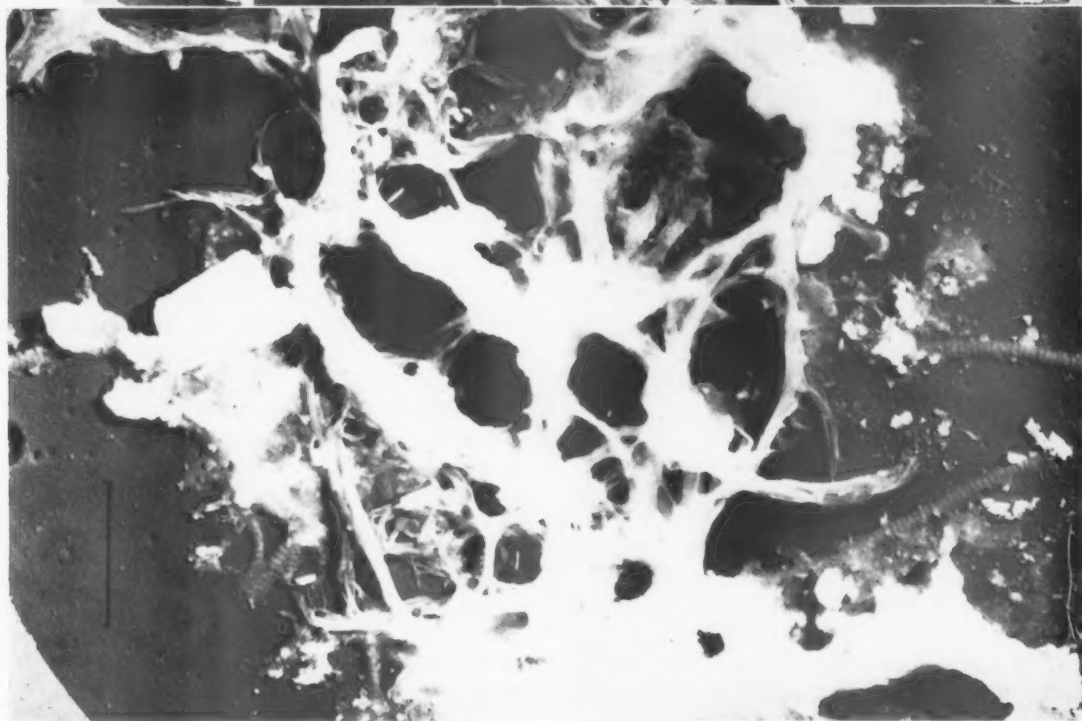
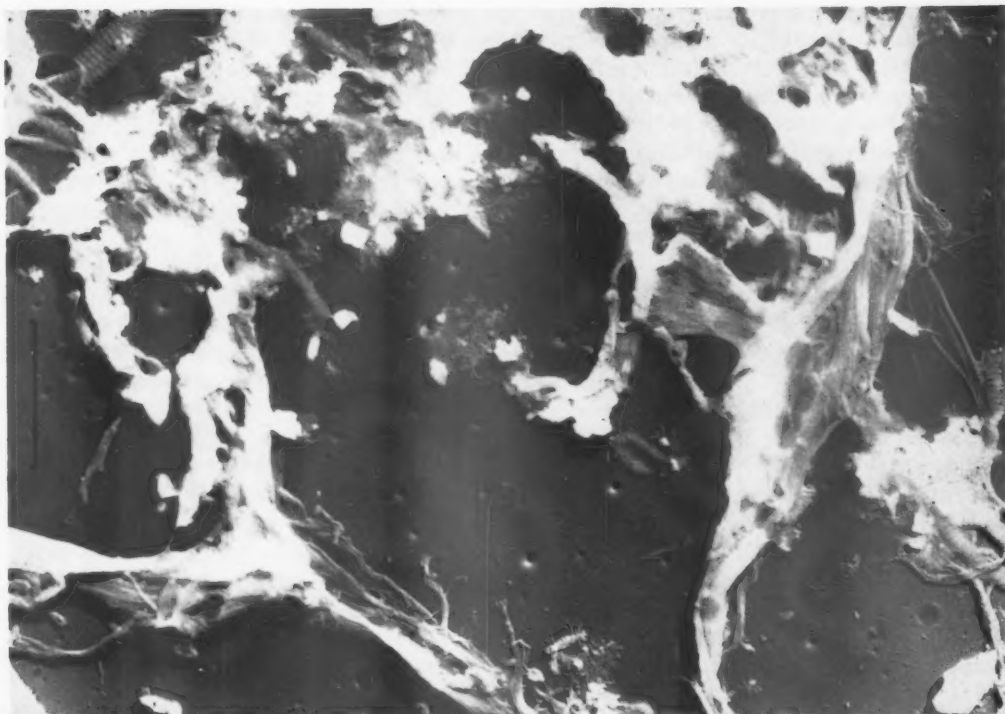
strates were relatively inert, those exhibiting excessive enzyme digestion were highly active, and the control group was intermediate between these two. This is demonstrated by the total "elastin" counts recorded at the foot of Table I. The count from the five substrates in the control group (13,446) was nearly  $3\frac{1}{2}$  times that for the six collagenase-resistant substrates (4,006). In contrast, the two substrates exhibiting excessive digestion by collagenase gave a slightly higher total (4,124) than the six indigestible derma.

(5) A 3-hr incubation with phthalate buffer alone (pH 5.0) gave a greater response in all the groups



Fig. 35.—Transformation structure (TS) from the 56-year-old control substrate (D15) after incubation with periodate in phthalate buffer (pH 5.0) for 3 hrs at 37° C. Most of the dense bundle can be visualized as "elastin".

than either periodate in phthalate buffer or borate buffer (pH 8.8) for 24 hrs at 37° C. These experiments in buffer alone were the *control* series for the periodate studies, and periodate was one of the first reagents described which apparently transforms collagen into elastin-like structures (Burton and others, 1955). However, the detailed scrutiny and exhaustive counting undertaken in the present investigation revealed that, though the periodate experiments *did* increase the "elastin" counts and produced a transformation picture, the buffer solutions *alone* gave a greater response in all cases. It is also noteworthy that this response occurred after only 3 hours' incubation, and that both periodate and phthalate buffer alone produced higher counts and more transformation pictures than the longer, 24-hr incubation with alkali. In addition, the phthalate buffer alone evoked a response even in two of the youngest subjects (D8 and D9), yet both periodate and alkali were



Figs 36 and 37.—Incubation of the control substrate from the infant (D12) for 3 hrs at 37° C. with periodate in phthalate buffer (Fig. 36) and in phthalate buffer (pH 5.0) alone (Fig. 37). These illustrate small areas from the almost continuous transformation picture seen after each of these treatments.

without effect. These as yet unexplained phenomena merit further study. It is possible that the addition of the 1 per cent periodate solution to the phthalate buffer produced a dilution effect or an alteration in ionic strength which decreased the ability of the reagent to break down collagen. Unfortunately insufficient dermal substrate remained to investigate this matter in detail.

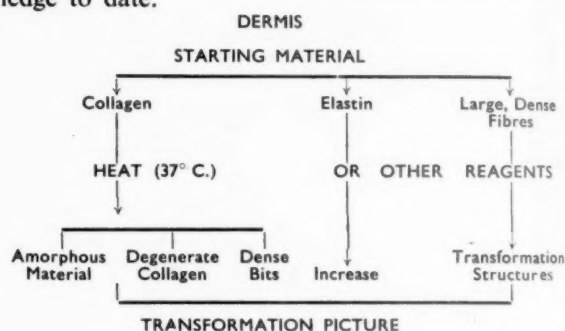
The paucity of the fine thread-like structures (Table I) following the action of all the reagents used in this study is in conformity with previous work (Keech and others, 1956) which demonstrated an increase in numbers as the pH value rose above 7.0. Most of the present experiments were conducted at pH 5.0 and 5.6, but incubation with borate buffer (pH 8.8) produced an increase in most of the substrates in Groups I and III. The appearance of structures closely resembling the manufactured networks (MN) described previously, show that they *can* occur at 37° C. although they were far less in comparison with the numbers seen after heating *above* body temperature, treatment with acetic acid, etc., as already reported (Keech and others, 1956). In the present investigation, only 65 of these manufactured networks were seen in the process of scanning a minimum of 120,000 fields. Their occurrence was sporadic, and bore no apparent relationship to age, treatment, or increase in "elastin".

It must be remembered that the starting materials used throughout comprised human dermis that had been "purified" by the method of Neuman (1949a, b) as shortened by Keech (1954a). This process involves prolonged extraction at 4° C. with 10 per cent. NaCl followed by N/15 Na<sub>2</sub>HPO<sub>4</sub>, to remove mucoproteins and interfibrillar material. It is unlikely that this would affect the original natural elastin, which is present in small quantities in all the starting materials. However, although Neuman claims that this procedure does not denature or alter the properties of collagen, recent work demonstrating the apparent transformation of collagen to elastin-like structures by alkali (Burton and others, 1955; Hall and others, 1955) throws doubt on this method of preparation. However, whatever the nature of the substrate after purification, does not invalidate the comparisons made in this study.

The lack of response to incubation with borate buffer (pH 8.8) exhibited by all the collagenase-resistant substrates, both biochemically (*vide infra*) and under the electron microscope, provides a clue to the uniform morphology of all the starting materials in this group (Tables I and III). The alkali used in Neuman's procedure may have removed the interfibrillar material without altering

the fibrils, thus accounting for the clean appearance of the collagen and the lack of amorphous material and dense bits (which are presumably derived from the products of collagen breakdown). This group's resistance to breakdown correlated with a lack of transformation into "elastin". However, in the two inert substrates in which collagen degeneration was induced by phthalate (D8 and D9 *vide supra*) the usual conversion to elastin-like material was found. This is in keeping with the hypothesis (Hall and others, 1955) postulating collagen breakdown as a prerequisite for the formation of "elastin" by rearrangement of the collagen components.

The following diagram offers an explanation for the morphological findings as based on our knowledge to date.



The starting materials of both fresh whole dermis and the "purified" dermis of all age groups contain collagen, a small quantity of naturally-occurring or fully-formed elastin, and large, dense, square-ended fibres. Prolonged heat alone, at or below body temperature, can produce evidence of early collagen degeneration in the substrates from children and young adults (Keech and Reed, 1957), the effect being markedly increased by the addition of reagents such as borate, periodate, or phthalate. Collagen degeneration is associated with an increase in amorphous material and dense bits, which are probably collagen breakdown products.

The amorphous material under the electron microscope may derive from two sources: the breakdown of the collagen fibrils themselves, or the interfibrillar material released from the bundles during the various treatments. It may vary, therefore, in chemical composition according to its origin. Since an increase in skin-type "elastin" only occurs in the presence of some degree of collagen breakdown, these structures could be formed from degraded collagen combined with varying amounts of amorphous material.

Another possible, though not probable, cause of the increase in fully-formed "elastin" would be the progressive fragmentation of the original elastin by



heat, breaking it up into a larger number of smaller pieces. This seems unlikely, as there was no noticeable decrease in the size of the structures counted after heat alone.

As mentioned above, it has already been reported that the large, dense, square-ended fibres present in all the starting materials are converted into transformation structures (Keech and Reed, 1957). Thus two pathways are postulated for the production of the elastin-like material which constitutes the transformation picture: the products of collagen degeneration combine with varying amounts of amorphous material to give fully-formed "elastin", and the large, dense, fibres give rise to the TS.

Both these pathways can occur after the application of heat alone (depending on the age of the dermis), but the process is greatly enhanced by reagents such as borate, periodate, and phthalate. That these two mechanisms need not necessarily react together or in the same degree, is illustrated in Group II. Heat alone produced a smaller increase in skin-type "elastin" in these collagenase-resistant substrates, but a greater increase in TS when compared with the control group (Table II). This difference in response is thus further evidence of the different reactivities of these two groups of collagen.

The results of biochemical investigations of the same dermal substrates were in general agreement with the electron microscope findings. Protein determinations after incubation with either borate buffer (pH 8.8) or potassium hydrogen phthalate buffer (pH 5.0) revealed a difference between the three groups. The substrates of average collagenase sensitivity gave results similar to those recently reported (Hall, 1956), *i.e.* a tendency for the amount of protein dissolved by alkali to decrease as the age of the subject increased. In contrast, the two collagenase-resistant substrates showed no significant breakdown by alkaline buffer, whereas the group which exhibited excessive digestion by collagenase gave higher readings than controls of comparable age. Similar results were found after incubation with phthalate buffer.

Chromatography showed that the total amino acid analysis was the same for all the groups, only the substrates in Group III took three times as long to hydrolyse as the others. The hydroxyproline content and shrinkage temperatures have recently been reported in detail (Hall and Reed, 1957). The hydroxyproline levels of all three groups were within the normal (mammalian) range, the values lying between 12.3-14.3 per cent. The micro-shrinkage temperatures (Borasky and Nutting, 1949), however, were quite distinct. The collagens

in the control group shrank over a range of 62 to 69.5° C., and the collagenase-resistant samples in Group II over a range of 72 to 79.5° C., whilst those in Group III, which were hypersensitive towards collagenase, shrank over the lower temperature range of 60 to 67° C. Thus, the distinct ranges of thermal shrinkage again reflected a difference between the three groups of collagen. In view of the drawbacks of Neuman's "purification" method already mentioned, no firm chemical explanation is possible. However, the most likely hypothesis is a difference in mucoid between the three groups.

The fact that the fibrils exhibit the morphological characteristics of normal collagen does not preclude a chemical difference. Morphological similarity does not necessarily mean chemical identity, as was recently demonstrated by Solomons and Irving (1956). They found that the availability of hydroxylysine and lysine polar side-chains was significantly greater in human dentin than in ox-hide collagen, and that this availability probably played a part in the combination of mineral material with the protein matrix of human dentin. This protein matrix has been shown under the light microscope (Widdowson, 1952) and under the electron microscope (Scott and Wyckoff, 1950; Yasuzumi and Obata, 1955) to consist of collagen morphologically identical with that found in human and animal skin. Thus, the collagenase-resistant collagens investigated in the present study may contain linkages which are either inaccessible to the action of collagenase and alkali, or, by some configurational variation from the normal collagen, are inaccessible to these two reagents. In the two collagenase-resistant substrates, which were mildly attacked by phthalate, one must assume that the linkages concerned in this type of reaction differ from those susceptible to collagenase and alkali.

The importance of the reactivity of collagen to collagenase has recently been shown by Ziffren and Hosie (1955), who demonstrated collagenase activity in canine pancreatic juice. Previous work (Keech, 1954b) suggested the presence of some substance capable of altering collagen in human dermis of all age groups. As mentioned at the beginning of this paper, rash-bearing and non-rash-bearing skin from a case of dermatomyositis differed in sensitivity towards collagenase. The answer to this riddle may be the key to the cause of so-called "collagen disease".

#### Summary

Further investigations were undertaken on six of the collagenase-resistant human dermal substrates and the two exhibiting excessive digestion by collagenase previously described by Keech (1955).



These were compared with five substrates showing average collagenase sensitivity.

Under the electron microscope, a significant increase in elastin-like structures was produced by phthalate buffer, periodate, and alkaline buffer, the degree of response depending on the age of the subject. The results paralleled the sensitivity of the substrate towards collagenase, the resistant group remaining unattacked by alkali and periodate, and only two of the six being mildly attacked by phthalate. In the remaining cases, phthalate buffer alone proved to be a more potent reagent for the apparent transformation of collagen to elastin-like structures than either periodate or alkali. Treatment in water at 37° C. produced a slight increase in "elastin", which was allowed for when the effect of incubation with chemical reagents was assessed. Only the latter gave a true transformation picture to "elastin". The tabulated results are based on the careful scrutiny of a minimum of 120,000 microscopic fields, and a total of 21,576 elastin structures were counted.

Biochemical studies confirmed the electron microscopic findings and the shrinkage temperature also reflected the different reactivity of these three groups of collagen.

It is a pleasure to thank Professor R. E. Tunbridge, O.B.E., for his sustained encouragement throughout this work, Dr. D. A. Hall and Mr. J. W. Czerkowski for performing the biochemical estimations, and Mr. A. Gill for the shrinkage temperature studies.

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#### Transformation du collagène en "élastine" dans les collagènes dermiques avec sensibilité variable à la collagénase

##### RÉSUMÉ

On procéda à de plus amples recherches sur six

substrata collagénase-résistants des dermes humains et sur les deux qui présentaient une digestion excessive par la collagénase, précédemment décrits par Keech (1955). On les compara à cinq substrata présentant une sensibilité moyenne à la collagénase.

Sous le microscope électronique, une augmentation significative des structures ressemblant à l'élastine se produisait par un tampon de phthalate, de périodate et un tampon alcalin, l'intensité de la réaction dépendant de l'âge du sujet. Les résultats étaient parallèles à la sensibilité du substratum à la collagénase, le groupe résistant n'étant pas attaqué par l'alcali et périodate, et seulement deux des six étant légèrement attaqués par le phthalate. Dans les cas restants, le tampon de phthalate seul s'est révélé un réactif plus puissant, pour la transformation apparente du collagène en structures semblables à l'élastine, que le périodate ou l'alcali. Le traitement par l'eau à 37° C. produisait une légère augmentation d'"élastine"; on en tenait compte en évaluant l'effet de l'incubation avec des réactifs chimiques. Seule cette dernière méthode donnait un vrai tableau de la transformation en "élastine". Les résultats catalogués sont basés sur l'examen soigné d'un minimum de 120.000 champs microscopiques et un total de 21.576 structures d'élastine a été compté.

Des études biochimiques ont confirmé les observations au microscope électronique et la température de contraction a reflété aussi la réactivité différente de ces trois groupes de collagène.

#### Transformación del colágeno en "elastina" en los colágenos cutáneos con sensibilidad variable a la colagenasa

##### SUMARIO

Se efectuaron investigaciones ulteriores sobre seis de los substratos de la piel humana resistentes a la colagenasa y sobre los dos que habían presentado una digestión excesiva por la colagenasa, anteriormente descritos por Keech (1955). Se los comparó a cinco substratos presentando una sensibilidad media a la colagenasa.

Bajo el microscopio electrónico, un aumento significativo de estructuras parecidas a elastina se produjo por un tapón de ftalato, de periodato y por un tapón alcalino, la intensidad de la reacción dependiendo de la edad del sujeto. Los resultados fueron paralelos a la sensibilidad del substrato a la colagenasa, el grupo resistente no siendo atacado por el alcali o el periodato, y sólo dos de los seis siendo ligeramente atacados por el ftalato. En los demás casos, el tapón de ftalato solo se reveló un reactivo más fuerte, para la transformación aparente del colágeno en estructuras parecidas a la elastina, que el periodato o el alcali. El tratamiento por el agua a 37° C. producía un ligero aumento de "elastina"; esto fué tomado en cuenta en la valoración del efecto de la incubación con reactivos químicos. Tan sólo este método daba el cuadro auténtico de la transformación en "elastina". Los resultados enumerados se basan en la investigación cuidadosa de un mínimo de 120.000 campos microscópicos y un total de 21.576 estructuras de elastina fué contado.

Estudios bioquímicos confirmaron las observaciones al microscopio electrónico y la temperatura de contracción también reflejó la reactividad diferente de estos tres grupos de colágeno.

## ATTEMPT TO ISOLATE A VIRUS FROM BIOPSY MATERIAL IN CASES OF RHEUMATOID ARTHRITIS

BY

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It was thought possible that rheumatoid arthritis might be caused by a virus and that in the course of the illness this virus might exist latently in the cells of the synovial membrane or of the peri-articular connective tissue.

Biopsies were therefore taken from the knee joints of two patients with active rheumatoid arthritis and raised erythrocyte sedimentation rates. One patient was a woman aged 56, who had suffered from rheumatoid arthritis for 8 years. The second was a woman aged 25, who had suffered from rheumatoid arthritis for 3 years.

The pieces of tissue, which were mostly fat and fibrous tissue with a little synovial membrane, were chopped up and made into plasma-clot roller-tube cultures (Robbins, Weller, and Enders, 1952). The medium used contained 5 per cent. horse serum, 5 per cent. beef embryo extract, and 90 per cent. bovine amniotic fluid. After 2 days' incubation, fibroblasts started to grow out round the pieces and these gradually formed large sheets. The sheets of fibroblasts from Case 1 continued to grow and look healthy for 8 weeks and thereafter gradually disintegrated. The sheets of fibroblasts from Case 2 looked healthy for 5 weeks, when areas began to appear near some of the explants in which the cells became granular and then degenerated. For 3 weeks these areas became bigger and then cells grew in from the surrounding cell sheet and the holes disappeared. The cultures eventually disintegrated as with Case 1.

Although the degeneration in Case 2 was considered to be non-specific, medium taken from the Case 2 cultures at the times that the degenerated areas were appearing, and medium and cells harvested 11 weeks after the Case 2 cultures were set up, were kept at  $-70^{\circ}\text{C}$ . and then inoculated into some of the cultures of Case 1 and into plasma-clot cultures of human embryo muscle and bone

and of monkey testis, all with good growths of fibroblasts. Medium and cells taken from the monkey testis cultures 3 and 6 weeks after inoculation were inoculated into cultures of Chang's human liver cells (Chang, 1954), and into plasma-clot cultures of human embryo muscle, bone, and lung. All these cultures appeared healthy for 2 to 3 weeks and then showed non-specific degeneration equally in the test and control cultures.

There was no evidence therefore that the tissues of these patients with rheumatoid arthritis contained a virus capable of causing degeneration of fibroblasts.

### Summary

An unsuccessful attempt is reported to isolate a virus from biopsy knee joint tissues taken from two patients with rheumatoid arthritis.

I am grateful to Dr. H. F. West for suggesting the investigation and for taking the biopsies, to Dr. D. A. J. Tyrrell for helpful guidance, and to Dr. Hamilton for supplying the human embryo tissues.

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### Tentative d'isoler un virus des prélèvements des cas d'arthrite rhumatismale

#### RÉSUMÉ

On rapporte une tentative sans succès d'isoler un virus des prélèvements des tissus de l'articulation du genou de deux malades atteints d'arthrite rhumatismale.

### Tentativa de aislar un virus del material de biopsia en casos de artritis reumatoide

#### SUMARIO

Se relata una tentativa infructuosa de aislar un virus del material de biopsia extraido de las articulaciones de la rodilla de dos enfermos con artritis reumatoide.

## DISTRIBUTION AND EXCRETION OF RADIOGOLD IN ANIMALS

BY

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Gold has been used in the treatment of rheumatoid arthritis for about 30 years and, although estimates of its value vary, many clinicians still consider it helpful in some cases. The way in which it produces clinical improvement is unknown and knowledge of its distribution and metabolism in man is fragmentary.

Freyberg, Block, and Levey (1941) and Block, Buchanan, and Freyberg (1941, 1942, 1944) reported upon the distribution of gold in the major organs of the rat after its injection in several chemical compounds, including some used therapeutically. Since then, sporadic papers have appeared, but the methods used in some studies have subsequently been criticized.

Radioactive isotopes of gold have not been used in this connexion. The isotopes commonly used as radiotherapeutic agents,  $^{198}\text{Au}$  and  $^{199}\text{Au}$ , decay so quickly that useful measurements of their distribution can only be made for a week or two. Since clinical improvement after gold may take several weeks to begin, more extended studies are clearly needed. The isotope  $^{195}\text{Au}$  has a half-life of 185 days and would be very suitable for such studies. However, because of its slow decay, retention at the site of injection or elsewhere in the body might produce a radiation hazard. It was necessary, therefore, to seek further information about the distribution of injected gold in animals before considering its use in human investigations. This paper records the distribution of gold in the tissues of rats, guinea-pigs, and rabbits up to 6 months after its injection as calcium aurothiomalate ( $^{195}\text{Au}$ ). Observations on excretion and on the effects of artificial inflammation are also reported.

### Material and Methods

(1) **Animals.**—Stock guinea-pigs and albino rats were used, their average weights being about 600 and 250 g.

respectively. The rabbits were young does weighing 1.5 to 2 kg. All animals received stock diet and water *ad lib.* throughout; they ate normally and remained in good health.

(2) **Radioactive Gold.**—The isotope  $^{195}\text{Au}$  was made in the Birmingham University cyclotron and synthesized into calcium aurothiomalate ( $^{195}\text{Au}$ ) at the Radiochemical Centre, Amersham.  $^{195}\text{Au}$  decays by orbital electron capture followed by gamma emission, 90 per cent. of which has an energy of 0.096 MeV ( $K/L = 5.5$ ) and 10 per cent. an energy of 0.129 MeV ( $K/L = 4.7$ ), to form the stable isotope  $^{195}\text{Pt}$  (Nuclear Data, 1950). The specific activity of the final product was about 9  $\mu\text{c./mg.}$  gold: it was diluted as needed with 5 per cent. gum acacia.

(3) **Procedures.**—Gold injections were given by micro-syringe and intradermal needle into the right quadriceps muscle. Rats received 0.05 ml., guinea-pigs 0.10 ml., and rabbits 0.20 ml. of a suspension containing approximately 6 mg. gold and 55  $\mu\text{c.}$  per ml.

Granuloma pouches were produced by two subcutaneous injections under anaesthesia, 5 days apart, of 15 ml. air in the interscapular region of rats, followed through the same needle by 1 ml. sterile 1 per cent. croton oil in arachis oil. All the pouches remained sterile and appeared to give the rats no discomfort.

Excreta were collected in screw-topped jars, whose activity was later compared with a standard in a "crown" of Geiger counters (Veall and Vetter, 1952). Carcasses were dissolved in fuming nitric acid, transferred to jars, and their activity similarly measured. Organs and tissues were dissolved in fuming nitric acid and the activity in 10-ml. volumes was determined in a scintillation counter. All except the largest specimens could be digested down to this volume. A light precipitate formed after digestion in some specimens with a high calcium content but this was found not to affect estimates of activity. Excess of fat remaining after digestion was removed and added to the appropriate carcass; fat regularly contained only traces of activity.

Inert carrier (gold chloride) was added to all specimens.

(4) The significance of differences between means was assayed by the "t" test for small samples:

$$t = \frac{\bar{x}_1 - \bar{x}_2}{\sigma_{\Delta}} \quad \sigma_{\Delta} = \sqrt{\frac{n_1 s_1^2 + n_2 s_2^2}{n_1 + n_2 - 2} \cdot \left( \frac{n_1 + n_2}{n_1 n_2} \right)}$$

(5) **Recovery Experiments.**—Radiogold was injected into five different organs which were then digested and their activity measured; an average of 97.3 per cent. was recovered (range 96.5-98.9). Eight carcasses were injected and processed; the mean recovery was 101.2 per cent. (92.5-113). On eight occasions, the radiogold was dropped on to the bottom of a rat cage and the excreta of five untreated animals were then collected from that cage for 4 days. The average recovery of activity was 91.2 per cent. (range 87.0-97.6).

A further indication of the degree of recovery is given by the groups of animals whose excreta were collected till death. Seven groups of rats gave a mean total recovery of 95.0 per cent. (range 84.9 to 105.2), and from eight rabbits the mean was 86.0 per cent. (range 77.8 to 90.2).

## Results

### Distribution after a Single Injection

Fig. 1 shows the average percentage of the dose of radioactivity found after various intervals at the site of injection in rats, guinea-pigs, and rabbits. Some activity was present at the injection site of every animal throughout the period of study. In all species an average of about 80 per cent. of the dose had left the injection site in the first 4 weeks; thereafter removal was much slower. Two rat quadriceps still retained 22 per cent. of the dose 24 weeks after injection and their presence in this small group explains its having a higher average activity than the 12-week group. The injection sites of the 4- and 12-week groups of guinea-pigs show a similar anomaly, the average activity being higher in the later group because of a single value of 43.6 per cent.

The percentage of the injected radioactivity which was found in some important organs after various

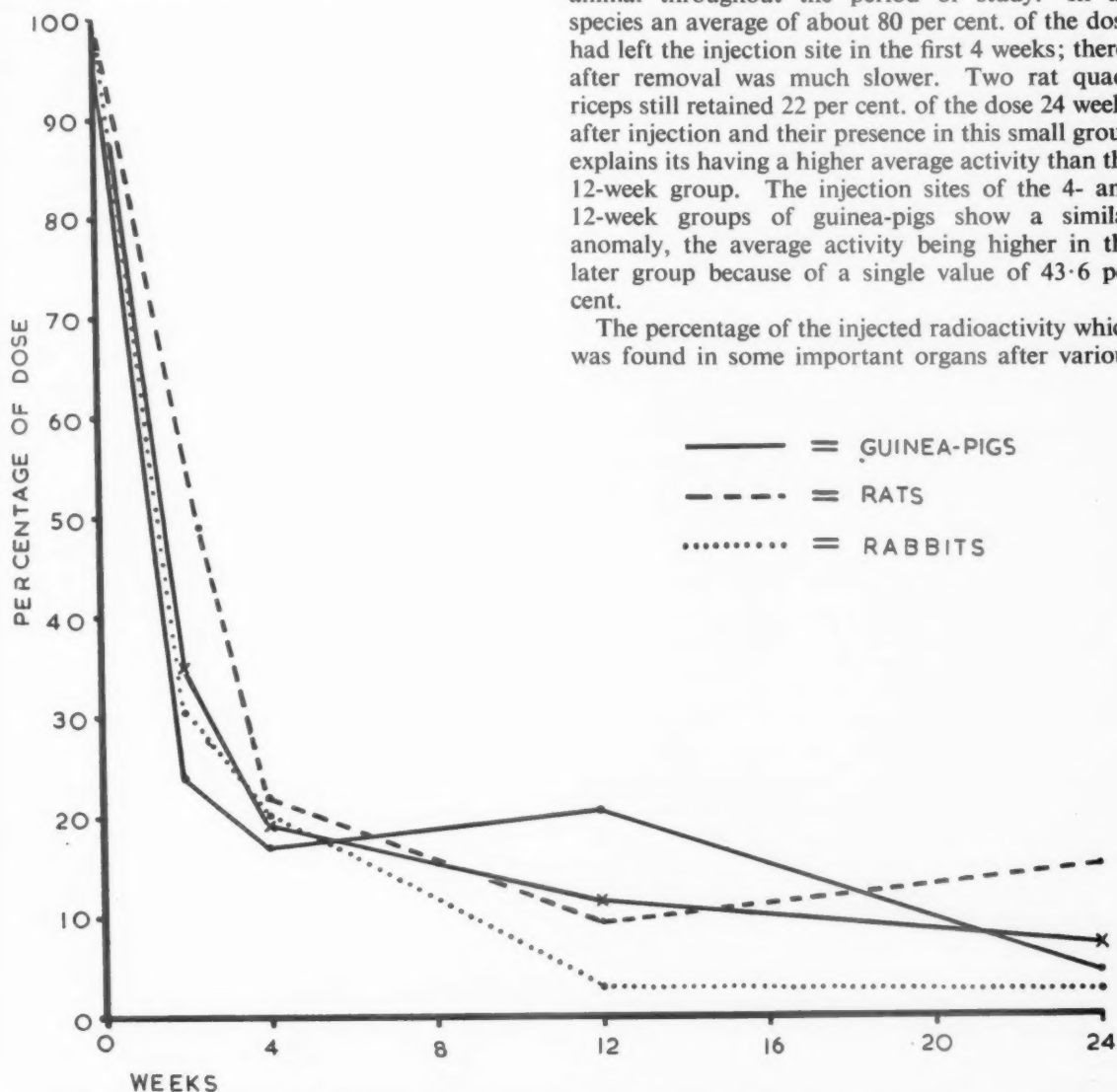


FIG. 1.—Mean percentages of injected dose recovered from site of injection in groups of animals after various intervals. Curve X—X represents the mean of the three species.



intervals is shown in Table I. The rat kidneys might contain up to 10 per cent. of the dose in the first 4 weeks and they remained the organs with the highest content of activity. In guinea-pigs and rabbits, kidney radioactivity was less and was roughly equal to that present in the liver. Spleen and lungs followed the liver in order of content but never contained more than 1 per cent. of the dose in any species.

The total radioactivity remaining in the body at 24 weeks varied from 5 to 10 per cent. in guinea-pigs and rabbits and from 13 to 37 per cent. in rats. As in the case of injection sites, the total body activity was greater in the 24-week group of rats than in the 12-week group. Nearly all organs showed their highest content of activity at 2 weeks; in a few instances the 4-week figure was slightly higher.

Table II (opposite) shows the relative concentrations of radioactivity in various rat tissues, expressed as percentage of the dose per gram of tissue. As the results in guinea-pigs and rabbits were in general the same, detailed tables of these species are omitted; notable differences are mentioned here.

The concentration at injection sites is not given, for the injected material remained fairly localized and any estimate of concentration would depend largely on the amount of inert surrounding muscle excised.

In all species individual results varied widely, so that in these small groups the coefficients of variation lay usually between 25 and 50 per cent. Unless it is stated otherwise, subsequent remarks refer to mean values.

In rats and rabbits the kidney at all times had the highest concentration of activity but after 2 weeks the guinea-pigs' spleen contained concentrations similar to those in their kidneys. The values for rat kidneys were regularly several times higher than those of the other species.

The spleen had the next highest concentration in all species. At 2 weeks, the only other tissues containing more than twice the carcass concentration were rat adrenal and guinea-pig liver. At 4 weeks, the values for rat adrenal, uterus, ovary, pancreas, and lymph gland, and for rabbit adrenal had risen to between three and eight times the carcass concentration. These increases were still

TABLE I  
PERCENTAGE OF DOSE IN VARIOUS SITES

Animals	Site	No. of Weeks after Injection							
		2		4		12		24	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Rats	Injection Site .. .. .	47.9	16.9	21.1	11.1	9.3	1.9	14.5	9.3
	Kidneys .. .. .	6.56	2.3	5.12	1.85	0.83	0.12	0.25	0.15
	Liver .. .. .	0.85	0.29	0.61	0.33	0.24	0.07	0.18	0.09
	Spleen .. .. .	0.36	0.15	0.22	0.08	0.06	0.013	0.02	0.01
	Lungs .. .. .	0.13	0.06	0.09	0.02	0.04	0.024	0.02	0.01
	Adrenals .. .. .	0.007	0.004	0.007	0.002	0.003	—*	0.002	—*
	Ovaries .. .. .	0.014	0.007	0.021	0.020	—	—	—	—
	Total in Animal .. .. .	67.0	14.9	37.4	11.3	13.5	2.2	24.8	9.5
	No. of Animals .. .. .	10		10		5		4	
Guinea-Pigs	Injection Site .. .. .	23.9	6.6	16.2	1.2	19.9	16.1	4.5	2.8
	Kidneys .. .. .	4.00	1.1	0.62	0.57	0.24	0.13	0.05	0.04
	Liver .. .. .	3.66	0.93	0.84	0.52	0.29	0.10	0.08	0.07
	Spleen .. .. .	0.20	0.04	0.11	0.03	0.041	0.10	0.007	0.003
	Lungs .. .. .	0.09	0.03	0.04	0.009	0.016	0.005	0.006	0.005
	Adrenals .. .. .	0.018	0.006	0.01	—*	0.006	—*	0.006	—*
	Total in Animal .. .. .	49.6	4.8	28.5	2.1	26.4	16.2	6.2	2.2
	No. of Animals .. .. .	4		4		4		4	
Rabbits	Injection Site. .. .. .	30.2	11.1	18.9	8.4	2.8		2.3	
	Kidneys .. .. .	3.69	0.36	2.05	0.7	0.86		0.15	
	Liver .. .. .	2.67	0.66	2.28	1.0	1.12		0.06	
	Spleen .. .. .	0.07	0.04	0.05	0.03	0.01		0.004	
	Lungs .. .. .	0.29	0.03	0.13	0.05	0.02		0.006	
	Adrenals .. .. .	0.005	0.001	0.003	0.001	0.001		<0.001	
	Ovaries .. .. .	0.008	0.002	0.006	0.001	0.003		<0.001	
	Total in Animal .. .. .	61.7	7.8	42.9	7.4	14.45		12.1	
	No. of Animals .. .. .	3		3		2		1	

In the case of bilateral organs, the total activity in both is given.  
\* = Pooled specimens.

TABLE II  
PERCENTAGE OF DOSE PER GRAM OF TISSUE IN RATS

Site	No. of Weeks after Injection							
	2		4		12		24	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Kidney .. .. .	2.83	1.0	2.46	1.0	0.321	0.066	0.086	0.056
Liver .. .. .	0.062	0.024	0.050	0.04	0.016	0.005	0.008	0.004
Spleen .. .. .	0.362	0.12	0.310	0.163	0.068	0.010	0.032	0.016
Lung .. .. .	0.077†	0.031	0.053	0.017	0.025	0.010	0.006	0.004
Submandibular gland ..	0.061†	0.031	0.048	0.023	0.008	—*	0.005	0.003
Adrenal .. .. .	0.113	0.049	0.260	0.023	0.054	—*	0.008	—*
Heart .. .. .	0.026†	0.006	0.024	0.006	0.006	0.002	0.003	0.001
Pancreas .. .. .	0.082†	0.036	0.116†	0.055	0.035	0.014	0.006	—*
Brain .. .. .	0.004†	0.002	0.004	0.004	0.002	0.001	0.002	0.002
Pituitary .. .. .	0.033	—*	0.057	—*	0	—	0	—
Testes .. .. .	—	—	—	—	0.014	0.006	0.012	0.004
Ovary .. .. .	0.103†	0.06	0.116†	0.043	—	—	—	—
Uterus .. .. .	0.112†	0.016	0.25	0.28	—	—	—	—
Skin .. .. .	0.051†	0.006	0.040	0.022	0.007	0.001	0.006	0.003
Femur .. .. .	0.026†	0.008	0.019	0.007	0.007	0.003	0	—
Knee joint .. .. .	0.048†	0.027	0.030	0.008	0.006	0.003	0.007	0.011
Lymph gland .. .. .	0.102†	0.033	0.130	—*	0.024	—*	0.022	—*
Jejunum .. .. .	0.075†	0.021	0.055†	0.025	—	—	0.007	0.003
Ileum .. .. .	0.059†	0.025	0.058†	0.022	—	—	0.003	0.005
Colon .. .. .	0.074†	0.023	0.053†	0.021	—	—	0.006	0.004
Quadriceps muscle ..	0.012†	0.001	0.012	0.004	0.002	0.001	0.001	0.001
Total Carcase .. ..	0.054	0.019	0.032	0.010	0.009	0.003	0.007	0.005
Number of Animals ..	10		10		5		4	

\* = Pooled specimens.

† = Five specimens only.

evident at 12 weeks in rat adrenal and pancreas and up to 24 weeks in rat lymph glands.

Average values in other tissues were never more than three times the carcase concentration. Activity was not concentrated by intestine or reproductive organs and the relatively large quantities of activity present in the liver (Table I) were due simply to its size and not to any special concentrating ability. Brain and voluntary muscle regularly contained concentrations of activity well below the carcase level. There was no evident localization of activity in joint tissues.

#### Excretion after a Single Injection

Excreta were collected from some rats, in groups of five, and from some rabbits individually. The daily rate of excretion is shown in Fig. 2 (overleaf), and the average quantities excreted appear in Table III (overleaf).

The rate of excretion reached its maximum about 6 days after injection, when up to 3 per cent. of the dose was excreted daily, and thereafter declined. Both species excreted about 40 per cent. of the dose in 4 weeks, the rates of excretion being remarkably similar.

#### Effect of Multiple or Repeated Doses

(1) *Multiple Doses.*—In two rabbits the quantity of radiogold usually given in one injection was divided into four parts and given into each triceps

and quadriceps muscle. When the rabbits were killed after 2 weeks the distribution of activity did not differ from that in animals given a single injection. All the muscles contained between 22 and 36 per cent. of the activity injected into them. Both the animals excreted about 34 per cent. of the dose in the 2 weeks after injection.

(2) *Single Active Dose followed by Inert Gold Injections.*—To observe any possible modifying effects of subsequent injections upon the fate of the first injection, four rats were given the usual dose of radiogold followed by three weekly injections of the same quantity of inert calcium aurothiomalate. Excreta were collected for 6 weeks and the animals were killed at 12 weeks. This group retained slightly more activity at the injection site and in the whole animal (means 14.0 and 18.4 per cent.) compared with the rats which had received only a single radiogold injection (means 9.3 and 13.5 per cent.); the kidneys, on the other hand, contained slightly less (0.60 compared with 0.83 per cent.). None of these differences is statistically significant and the content and concentration of activity in other tissues were closely similar to those found in the rats given a single radiogold injection.

Excretion of the initial radiogold injection was unaffected by the subsequent giving of inert gold (Table III). The total 6 weeks' excretion was 46.8 per cent., almost the same as the average for rats given a single active injection only.

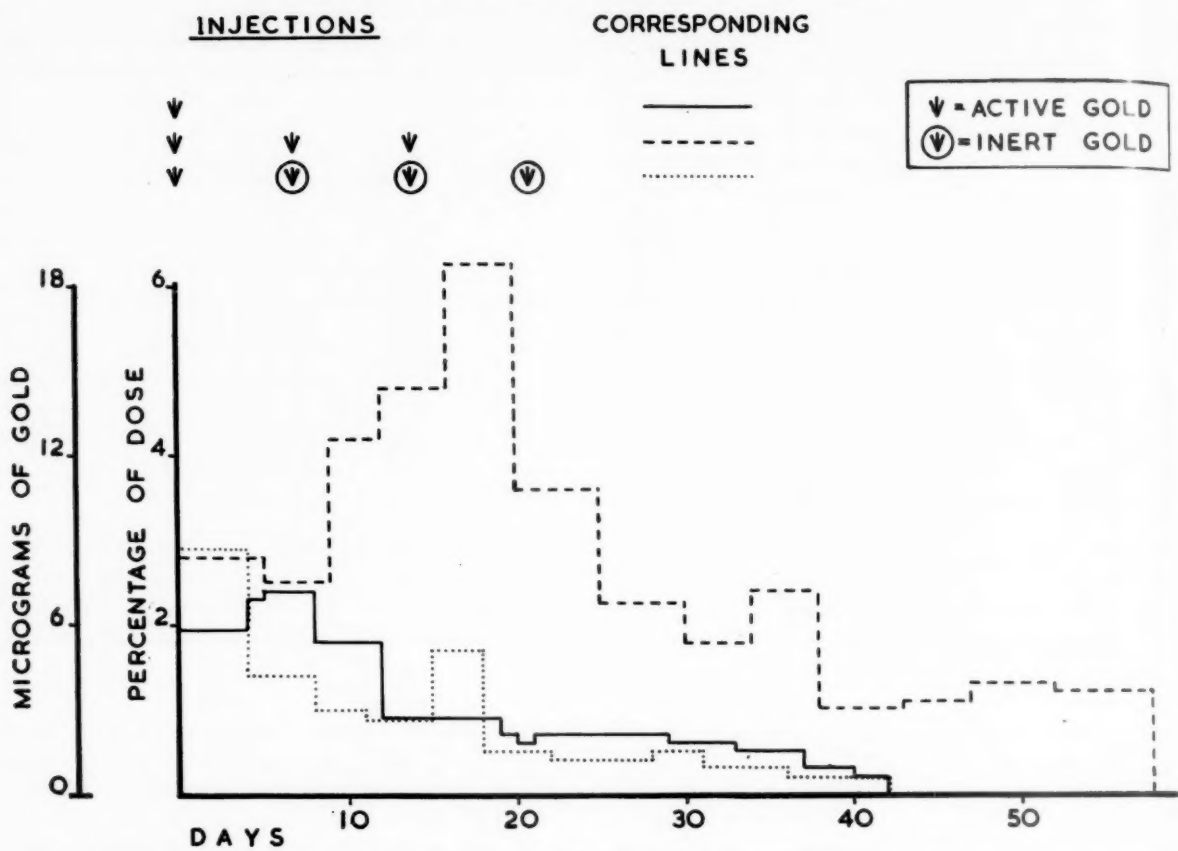


FIG. 2.—Excretion of radioactivity by groups of rats after radiogold injection, shown as mean percentage of dose excreted per rat per day. Results are given after a single dose of radiogold, after three doses at weekly intervals, and after one radioactive dose followed by three weekly doses of the same quantity of inert calcium aurothiomalate.

TABLE III  
PERCENTAGE OF INJECTED RADIOGOLD RECOVERED IN EXCRETA

Animal	Dosage	No. of Weeks after Injection					
		0-2		2-4		4-6	
		Mean	S.D.	Mean	S.D.	Mean	S.D.
Rabbit	Single Dose of Radiogold .. ..	28.0	5.9	13.1	3.0	—	—
	No. of Animals .. ..	8		3		—	
Rat	(i) Single Injection of Radiogold .. ..	26.2		12.7		6.1	
	No. of Animals .. ..	25		15		5	
	(ii) Single Injection of Radiogold then Three of Inert Gold .. ..	28.5		13.4		4.9	
	No. of Animals .. ..	5		5		5	
	(iii) Granuloma Pouch (Radiogold 1 week later) .. ..	41.3		26.1		—	
	No. of Animals .. ..	10		5		—	
	(iv) Granuloma Pouch (Radiogold 4 weeks later) .. ..	33.0		12.2		—	
	No. of Animals .. ..	4		4		—	

Excreta were collected from groups of four or five rats and singly from rabbits; standard deviations are therefore only given for rabbits.

(3) *Three Weekly Injections of Radiogold.*—Five rats were given three injections of radiogold at weekly intervals into the same quadriceps muscle. Excreta were collected for 6 weeks and the animals were killed after 12 weeks. At the injection site an average of 13.7 per cent. of the total dose was recovered, compared with 9.3 per cent. in rats given a single injection, and the whole animals contained 25.6 per cent. of the dose compared with 13.5 per cent. Nearly all the tissues of the three-dose rats contained concentrations of activity two or three times greater than those found in single-dose animals, but the pattern of distribution was unaltered. In tissues other than kidney, spleen, and pancreas, the concentration of activity was less than three times the general carcass level; activity in the brain was well below that in the carcass.

In 6 weeks, 49.6 per cent. of the total injected activity was excreted, almost the same as the average after a single dose. The course of excretion, depicted in Fig. 2, shows that stepwise increases in output followed each injection. The rate of excretion fell rapidly when injections ceased but throughout the period of study remained considerably higher than that observed after a single dose.

#### Effect of Artificial Inflammation

Granuloma pouches were produced in rats and one week after the second irritant injection some of them received a single dose of radiogold. Groups were killed 2, 4, and 12 weeks after the gold injection. Another group was given radiogold 4 weeks after the second irritant injection and was killed 4 weeks later. Table IV summarizes the distribution

of the radioactivity; Table V (overleaf) shows the relative concentrations in different tissues.

(1) *Radiogold One Week after the Second Irritant Injection.*—In this group of animals, activity left the site of injection much more quickly than in normal animals. All the differences are significant ( $p = <0.01$  at 2 and 4 weeks, and  $0.02 > p > 0.01$  at 12 weeks). An average of 15 per cent. of the dose remained at the injection site after 2 weeks compared with 48 per cent. in normal rats. The activity in the kidneys, liver, and spleen was greater in the rats with pouches than in normal animals, but only in the case of the kidneys at 12 weeks did the difference reach the significance level ( $p = 0.05$ ). The total activity present in the body at 2 weeks was reduced in the "pouch" rats ( $p = <0.01$ ), but at 4 and 12 weeks the differences were unimportant.

The granuloma pouch contained about 1 per cent. of the injected activity at 2 and 4 weeks, the highest single value being 2.5 per cent. In four animals the quantity of activity present in the wall and the fluid content of the pouch was compared and appeared roughly equal.

The relative concentrations of radioactivity in various tissues appear in Table V. Comparison with normal animals (Table II) reveals that the rats with pouches had higher concentrations in the kidney, liver, spleen, and heart at 2, 4, and 12 weeks. The increase was never greater than two-fold and only reached the significance level ( $p = 0.05$ ) in the case of the spleen at 2 and 4 weeks. The carcasses of the "pouch" animals had a higher concentration of activity after 4 and 12 weeks ( $p = <0.01$  in each case). There was no increase in intestinal or reproductive tissues.

TABLE IV  
PERCENTAGE OF INJECTED RADIOACTIVITY IN ORGANS OF RATS WITH GRANULOMA POUCHES

Radiogold Given .. ..		1 Week after Last Irritant Injection						4 Weeks after Last Irritant Injection	
Weeks after Giving Radiogold .. ..		2		4		12		4	
No. of Animals .. ..		10		5		4		4	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Site	Injection site ..	15.0	8.6	1.92	1.7	4.22	3.9	35.75	9.9
	Kidneys ..	7.67	2.62	6.26	0.58	1.49	0.51	5.97	0.25
	Liver ..	0.88	0.62	0.96	0.14	0.35	0.08	0.55	0.12
	Spleen ..	0.42	0.16	0.30	0.03	0.093	0.041	0.27	0.12
	Lungs ..	0.15†	0.05	0.098	0.017	0.050	0.019	0.12	0.06
	Adrenals ..	0.085	—*	0.010	0.002	0.007	—*	0.009	0.003
	Ovaries ..	0.016†	0.010	0.016	0.006	0.004	0.001	0.017	0.004
	Granuloma pouch ..	0.94	0.36	0.99	0.92	0.031	0.027	0.055	0.032
Total in Animal ..		44.3	12.8	41.6	5.7	17.8	2.4	57.1	15.6
Amount Excreted ..		45.1†	—*	63.6	—*	—	—	46.4	—*

\* = Pooled specimens.

† = Five specimens only.



TABLE V

RELATIVE CONCENTRATIONS OF INJECTED RADIOGOLD IN RATS WITH GRANULOMA POUCHES

Radiogold Given .. ..		1 Week after Last Irritant Injection						4 Weeks after Last Irritant Injection	
Weeks after giving Radiogold .. ..		2		4		12		4	
No. of Animals .. ..		10		5		4		4	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Site	Kidney .. ..	3.84	1.41	2.91	0.35	0.710	0.32	2.81	0.48
	Liver .. ..	0.089	0.071	0.086	0.010	0.027	0.006	0.043	0.006
	Spleen .. ..	0.514	0.180	0.418	0.063	0.120	0.047	0.243	0.22
	Lung .. ..	0.098†	0.012	0.070	0.015	0.020	0.005	0.057	0.019
	Heart .. ..	0.042†	0.008	0.030	0.006	0.009	0.002	0.023	0.004
	Adrenal .. ..	0.121	0.051	0.146	0.021	0.084	—	0.100	0.030
	Pancreas .. ..	0.055†	0.036	0.136	0.022	0.075	0.032	0.108	0.070
	Submandibular gland	—	—	0.045	0.009	0.025	0.031	0.038	0.010
	Lymph gland ..	0.091†	0.045	0.187	—	0.056	—	0.121	0.042
	Ovary .. ..	0.095†	0.053	0.109	0.025	0.026	0.014	0.080	0.014
	Uterus .. ..	0.066†	0.050	—	—	—	—	0.193	0.21
	Jejunum .. ..	0.056†	0.011	—	—	—	—	0.045	0.013
	Ileum .. ..	0.040†	0.015	—	—	—	—	0.038	0.007
	Colon .. ..	0.058†	0.019	—	—	—	—	0.038	0.011
	Brain .. ..	—	—	0.094	0.001	0.003	0.001	0.003	0.001
	Pituitary .. ..	—	—	0.005	—	0	—	0.071	0.036
	Skin .. ..	—	—	0.061	0.034	0.016	0.009	0.049	0.011
	Shaft of femur ..	—	—	0.024	0.007	0.005	0.004	0.012	0.001
	Quadriceps muscle	—	—	0.014	0.005	0.005	0.005	0.010	0.005
	Granuloma pouch	0.206	0.260	0.183	0.170	0.074	0.069	0.099	0.028
Total Carcase .. ..		0.059	0.024	0.103	0.015	0.038	0.012	0.047	0.019

Figures denote percentage of dose per g. tissue.

\* = Pooled specimens.

† = Five specimens only.

Excretion of the injected activity was followed up to 4 weeks (Table III). In the first and second 2-week periods, the rats with pouches excreted 13 and 15 per cent. more of the dose than the averages for healthy animals: these differences could easily be fortuitous ( $0.2 > p > 0.1$  for the first 2 weeks). The average maximum rate of excretion, 3.7 per cent. of the dose per day, occurred within 4 days of injection and was higher than in normal rats (2.8 per cent. per day).

(2) *Radiogold Four Weeks after the Second Irritant Injection.*—In these four rats, killed 4 weeks after the dose of radiogold, more activity was present at the site of injection and in the kidneys than in normal rats after the same interval. The difference could readily be due to chance with such a small sample and other tissues showed no material alteration in content or concentration. The total recovery of activity from the animal bodies was significantly greater than normal in these "pouch" rats. Their excretion was also slightly but insignificantly higher.

#### Discussion

This investigation, in which the distribution and excretion of gold in animals were estimated by measuring radioactivity after the injection of radiogold as calcium aurothiomalate ( $^{195}\text{Au}$ ), has confirmed in general the results of previous workers.

Block and others (1941, 1942, 1944) reported upon the distribution of gold in some major organs of the rat after the injection of various compounds, using a chemical method of estimation (Block and Buchanan, 1940, 1942). Calcium aurothiomalate was one of the compounds studied and we also used it for the present investigation, since it is the gold preparation which we usually employ therapeutically. The two series are not, however, wholly comparable, for we gave a single dose of a suspension in an aqueous medium, containing 0.3 mg. gold, whereas Block and others (1944) gave a daily dose of an oily suspension containing 1 mg. gold for 14 days and expressed their results in terms of days after the last injection.

Because of the different modes of administration, it might be expected that Block's results 15 days after ceasing injections would lie between our figures obtained 2 and 4 weeks after a single dose. In fact, the proportions of the dose recovered from the whole body, injection site, liver, and spleen of Block's rats are close to our figures for 4 weeks; their kidneys, however, contained considerably less gold than our rats at 4 weeks; 12 weeks after injection, when the effects of different dosages were presumably less important, the average total body content was virtually identical in the two series, being about 13 per cent. of the dose.

In our series, the distribution of radioactivity in the tissues was essentially the same in rats, guinea-pigs, and rabbits, and the excretion by rats and rabbits was remarkably similar. The lack of differences between species in handling doses of gold equivalent to those used in man somewhat enhances confidence in predictions from these experiments of radiation hazards from the use of  $^{195}\text{Au}$  in man.

It appeared at first that removal of activity from the site of injection might follow a simple exponential curve, but after 4 weeks, when about 80 per cent. of the dose had left the injection site, the rate of removal slowed greatly (Fig. 1). The reason for this is obscure. One possibility, that the injected material became encapsulated by fibrous tissue, can be excluded, since autoradiographs show no evidence of fibrosis around the foci of activity 6 months after injection. In two rats, four guinea-pigs, and one rabbit, killed after 24 weeks, between 2 and 9 per cent. of the dose remained at the injection site and a further 1 to 10 per cent. was recovered from the other tissues of the body. In two rats, however, 22 per cent. of the dose was still present at the injection site 24 weeks later. The possibility of this persistence in the injected muscle may well limit the use of this isotope in man.

Of the organs and tissues examined, the kidneys were at all times pre-eminent in content and concentration of radioactivity. Presumably this indicates their predominant role in excretion. We did not estimate urinary and faecal elimination of radioactivity separately, but the concentration of activity in the wall of the gut was never more than twice the average concentration in the carcase tissues. It would seem that faecal elimination was less important in our rats than in Block's; about three-quarters of the gold excreted by his rats during the 2 weeks of injections was contained in the faeces.

No other organ contained any major quantity of activity. Most tissues had attained their highest concentration of activity 2 weeks after injection, the level at 4 weeks being slightly lower; in a few tissues, the peak was not reached until 4 weeks. By 24 weeks, the kidney tissue was the only one to contain a concentration of activity markedly different from the carcase level. In the early weeks after injection, lymphoid tissue (spleen and lymph gland) and, to a lesser extent, the parenchymatous organs in general appeared to concentrate activity slightly. There was no special concentration by joint tissues; the brain and voluntary muscle contained less than the general average.

Excretion was closely similar in our rats and rabbits, about 40 per cent. being eliminated in the 4 weeks after injection. Block's rats excreted

40 per cent. of the total dose during the 14 days in which they had daily injections. Although we did not measure excretion beyond 6 weeks, the continuing slow mobilization of gold from the injection site might be expected to lead to the excretion of small amounts for long periods. Freyberg and others (1941), in fact, were able to detect gold in the urine for many months after its therapeutic injection in man.

The distribution of a single dose of radiogold was not altered by subsequent administration of the same compound of inert gold nor was excretion impaired. Thus there is nothing to suggest that gold therapy after the use of radiogold for investigations would increase the radiation hazard in man. With the doses employed, no upper limit to excretion was demonstrated. Three weekly injections were each followed by a proportionate increase in output. If the figures for excretion after a single dose are used to make an estimate of the excretion to be expected after three weekly doses, calculation shows that about 43 per cent. should be eliminated in the first 6 weeks. In fact, the rats given three weekly doses excreted 49.6 per cent. in this time, suggesting that excretion is proportional to total body content, and confirming the absence of an upper limit to excretion at this dosage level.

Since no animal equivalent to rheumatoid arthritis exists, we chose the granuloma pouch technique of Rindani and Selye (1953) to study the possible effects of granulomatous inflammation upon radiogold distribution. The technique produces a sac composed of granulation tissue. In the early stages, the wall consists of a thin necrotic zone outside which is a thicker layer of proliferating fibroblasts and capillaries with a light round cell infiltration. The necrotic layer and the round cells in time disappear, leaving a wall of young fibrous tissue containing some capillaries and residual fat lobules.

In its early stages the presence of this lesion appeared to accelerate the metabolism of gold. When radiogold was given a week after the last irritant injection, the rates of excretion of radioactivity and its removal from the site of injection were considerably enhanced. The increased rates only obtained for the first 2 weeks, however, the levels thereafter returning to those observed in normal animals. When gold was given a month after the production of inflammation, the augmented rates were not observed. Human rheumatoid arthritis, in which inflammation is chronic and often quite mild, might thus be expected to influence the radiation hazard from  $^{195}\text{Au}$  relatively little; if anything, its tendency would be to reduce the hazard.

The pattern of radiogold distribution was not altered by the presence of inflammation. In most tissues, the average content of activity was higher than in normal animals by about 50 per cent., though individual differences could readily have been fortuitous. The inflammatory tissue of the granuloma pouches contained material quantities of activity, the concentration per gram of tissue at 2 weeks being higher than that of all other tissues except kidney and spleen. This perhaps favours the idea that gold exerts a local effect on inflamed tissues rather than an indirect general effect.

### Summary

Calcium aurothiomalate ( $^{195}\text{Au}$ ) was given intramuscularly to rats, guinea-pigs, and rabbits, in doses equivalent in terms of body weight to those used in man.

The distribution of radioactivity in important tissues was followed for periods up to 24 weeks and the excretion for shorter periods.

Variations among the animals of one species were considerable: major differences between species were not apparent.

Four weeks after injection, an average of 20 per cent. of the dose remained at the site of injection and about 40 per cent. had been excreted. Up to 22 per cent. might, however, be found at the site of injection after 24 weeks.

The kidneys concentrated activity considerably, and other tissues to a much less extent.

Distribution and excretion were unaffected by splitting the dose of radiogold or by giving inert gold subsequently. A stepwise increase of excretion followed three weekly radiogold injections; the pattern of distribution was unaltered.

The presence of a recent granuloma pouch appeared to accelerate absorption of radiogold from the site of injection and its excretion.

We wish to thank the Medical Research Council for a grant to purchase the radiogold. We are much indebted to Dr. J. C. Charlton, who synthesized the required compound, and to Dr. D. P. Page Thomas, who was responsible for the care and injection of many of the animals. We also thank Dr. G. D. Kersley for encouragement and advice, Dr. G. Herdan for statistical guidance, and Mr. D. Tovey for invaluable assistance.

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### Distribution et excretion d'or radioactif chez les animaux

#### RÉSUMÉ

On a administré par voie intramusculaire de l'aurothiomalate de calcium ( $^{195}\text{Au}$ ) à des rats, des cobayes et des lapins, en doses équivalentes, relativement au poids du corps, à celles employées chez l'homme.

La distribution de la radioactivité dans les tissus importants fut observée durant des périodes allant jusqu'à 24 semaines et l'excrétion durant des périodes plus courtes.

Les variations parmi les animaux d'une même espèce furent considérables; des différences majeures entre les espèces ne furent pas apparentes.

Quatre semaines après l'injection, une moyenne de 20% de la dose se trouvait encore au point d'injection et environ 40% avait été excrétée. On pouvait cependant trouver jusqu'à 22% au point d'injection après 24 semaines.

Il y avait une considérable concentration de radioactivité dans les reins et beaucoup moins dans les autres tissus.

La distribution et l'excrétion ne furent pas affectées par la division des doses d'or radioactif ou par l'administration subséquente d'or inerte. Trois injections hebdomadaires d'or radioactif provoquèrent une augmentation au pas de l'excrétion; le tableau de distribution ne fut pas modifié.

La présence d'une poche granulomateuse récente semblait accélérer l'absorption de l'or radioactif du point d'infection, ainsi que son excrétion.

### Distribución y excreción de oro radioactivo en animales

#### SUMARIO

Aurothiomalato de calcio ( $^{195}\text{Au}$ ) fué administrado por vía intramuscular a ratas, cobayos y conejos, en dosis equivalentes, relativamente al peso del cuerpo, a las empleadas en el hombre.

La distribución de la radioactividad en los tejidos importantes fué observada durante periodos extendiéndose hasta 24 semanas, y la excreción durante periodos más cortos.

Las variaciones entre los animales de la misma especie fueron considerables; diferencias mayores entre especies no fueron aparentes.

Cuatro semanas después de la inyección, un promedio del 20% de la dosis encontrábase todavía en el sitio de la inyección, y cerca del 40% habiendo sido eliminado. Fué sin embargo posible encontrar hasta a un 22% en el sitio de la inyección al cabo de 24 semanas.

Hubo una considerable concentración de radioactividad en los riñones y mucha menos en los demás tejidos.

La distribución y la excreción no fueron afectadas por la división de las dosis de oro radioactivo o por la administración subsecuente de oro inerte. Tres inyecciones semanales de oro radioactivo provocaron paso a paso un aumento de la excreción, sin modificar el cuadro de distribución.

La presencia de una bolsa granulomatosa reciente parecía acelerar la absorción del oro radioactivo del sitio de inyección, así como su excreción.



# A SURVEY OF RHEUMATOID ARTHRITIS IN WEST CORNWALL

## A REPORT TO THE EMPIRE RHEUMATISM COUNCIL

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(RECEIVED FOR PUBLICATION MAY 25, 1957)

### I. INTRODUCTION

In the autumn of 1955, I was asked by the Scientific Advisory Committee of the Empire Rheumatism Council to carry out a survey of the prevalence of rheumatoid arthritis in a representative community in Cornwall. Some 250 homes were visited to establish a clinical diagnosis and also a similar number of homes of control families. At the same time information was collected which it was thought might have a bearing on the aetiology of the disease.

### II. SUMMARY OF PREVIOUS SURVEYS

(1) **British Isles.**—A survey was carried out in 1922 by some 49 general practitioners scattered throughout England and Wales, with aggregate lists of 90,891, who recorded all insured patients consulting them for "rheumatic conditions". A high prevalence of rheumatic complaints was found in the North-West of England, but this excess was due largely to osteo-arthritis and lumbago. When rheumatoid arthritis alone was considered, the incidence was found to be relatively high in the Southern half of England (Ministry of Health, 1924).

The Department of Health, Scotland (1945) collected numbers of insured persons off work and certified as suffering from any form of articular rheumatism from the Annual Reports for the years 1932-37 (pub. 1934-39). This sample is heavily weighted with men, the women in the younger age groups numbering only one-third of the total.

Stocks (1949) analysed sickness rates for rheumatism from the Wartime Social Service Survey for the years 1944-47. This survey was carried out monthly, some 45,000 people between the ages of 16 and 65 being visited annually. The sample was carefully distributed to cover the whole country and all grades of society.

Lawrence and Aitken-Swan (1952) and Kellgren, Lawrence, and Aitken-Swan (1953) made a survey of rheumatic complaints recalled over a period of 5 years before interview amongst miners in the Manchester coalfields, and also investigated a 1 in 10 house sample in the town of Leigh, Lancashire. A group of the patients interviewed in the course of this survey were reviewed 5 years later (Kellgren and Lawrence, 1956).

Miall (1955), working with Cochrane, Cox, and Jarman (1955), carried out a clinical, x-ray, and pathological survey of some sixty cases of rheumatoid arthritis amongst miners in the Rhondda Fach.

Logan (1953) searched the records of a group of eight general practitioners and from these estimated the prevalence of rheumatoid arthritis in a mixed population of 21,092; this work is the most comparable with the present survey.

The relevant results of these earlier surveys are set out in Table I (overleaf).

Mortality rates are of no use in estimating the prevalence of rheumatoid arthritis, but may be of some value in estimating the distribution of the disease. The Registrar-General's mortality figures for rheumatoid arthritis in the British Isles for the years 1950-55 are shown in Table II (overleaf). It will be noted that the lowest rate is that in England and Wales, that in Eire being by far the highest. With the exception of Northern Ireland, there has been a tendency for rates to rise during the 6 years under consideration.

(2) **World Distribution.**—Earlier writers seem to have had the impression that rheumatoid arthritis is essentially a disease of temperate climates. For example, Bach (1935) estimated that it was twenty times more prevalent in Northern Europe than in the tropics.



## PREVIOUS SURVEYS OF PREVALENCE

Date	Authors	Type of Sample	Age Group (yrs)	Diagnostic Criteria
1924	Ministry of Health	State insurance patients of 43 English and three Welsh general practitioners	16-65 (See Note 2)	General practitioners' consultation classified into nine rheumatic groups
1945	Department of Health Scotland	Incapacity due to chronic rheumatism amongst all insured personnel	16-65	Sickness certificates
1949	Stocks	Random population samples of general population, taken monthly over the year	16-65	Self diagnosis
1952	Lawrence and Aitken-Swan	Miners and sample of population of Leigh, Lancs.	16+ but more than half in 20-50 age group	"Complaints" over 5-year period in reply to questionnaire and clinical examination
1953	Kellgren, Lawrence, and Aitken-Swan	Random sample of Leigh, Lancs.	15+	"Complaints" at time of interview and clinical examination
1953	Logan	General practitioner records—eight doctors	16+	Entry on doctor's cards
1955	Miall	Males in Welsh mining village where progressive massive fibrosis was known to be prevalent	16+	Characteristic history of polyarthritis of peripheral joints with or without residual physical signs, supported by: x-ray evidence or positive Rose test
1956	Kellgren and Lawrence	Random sample of Leigh, Lancs.	55-64	Clinical, x-ray, and blood agglutination

Note 1: Prevalence rates refer to moderate and severe cases.

Note 2: Age group of population at risk unknown, but assumed to be the same as that of Approved Societies of England and Wales:

## ESTIMATED AGE DISTRIBUTION OF POPULATION AT RISK

Age Groups (yrs)	16-24	25-34	35-44	45-54	55-64	Over 65	Total
Per 1,000 Males	260	256	212	156	92	24	1,000
Males in Population at Risk	15,079	14,847	12,296	9,048	5,336	1,392	57,998
Per 1,000 Females	456	271	145	80	40	8	1,000
Females in Population at Risk	14,999	8,914	4,769	2,631	1,316	263	32,893

TABLE II  
DEATH RATES FROM RHEUMATOID ARTHRITIS  
PER 100,000 POPULATION  
BRITISH ISLES, 1950-1955

Population	1950	1951	1952	1953	1954	1955
England and Wales	1.6	1.7	1.5	1.7	2.0	2.3
Scotland	1	1	2	2	3	3
Northern Ireland	3.2	3.8	3.9	2.3	2.0	2.3
Eire	3	4	4	5	5	5

Table III (opposite) shows figures from the World Health Organization Epidemiological and Vital Statistics Reports (1948-50), and gives the average

mortality rates for the 3 years 1947-49 in countries recording more than a hundred deaths a year. These rates are based on the classification used in the 5th Decennial Revision of the International List of Causes of Death and Mortality (International Institute of Statistics and Health Organization of the League of Nations, 1938), and are thus not comparable with the rates given in Table II.

In general, the mortality rates are seen to be high in the British Isles and the Northern European countries, and low in the Southern European and Mediterranean countries. The U.S.A. and the British Dominions of Canada, New Zealand, and Australia show comparatively low rates.

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RHEUMATOID ARTHRITIS

Size of Sample (No. of cases in brackets)			Notes	Prevalence Rate (per 1,000)		
Male	Female	Total		Male	Female	Total
58,169 (83)	32,720 (97)	90,891 (180)	Female sample heavily weighted in 16-24 age group (see Note 2). Incidence highest in Scotland and Eastern areas of England	1.43	2.95	2.0
			Female sample heavily weighted in younger age group	3.6	3.7	3.7
42,140 (109)	51,692 (354)	93,832 (463)		2.6	6.6	4.9
3,673 (43)	3,085 (136)	6,758 (179)		11.7	36.6	26.4
1,298 (18)	1,600 (52)	2,898 (70)		13.9	32.5	24
8,994 (23)	12,048 (88)	21,092 (111)		2.55	7.3	5.2
9,430 (66)			Of this group of cases 20 per cent. showed no x-ray changes and 15 per cent. a negative Rose differential agglutination test	7.0		
173 (3)	207 (7)	380 (10)	The survey was planned to discover the prevalence of x-ray and blood agglutination changes in the general population (see Note 1)	17.3	33.7	26.3

TABLE III  
DEATHS FROM CHRONIC RHEUMATISM AND GOUT  
PER 100,000 INHABITANTS

Country	1947		1948		1949	
	No.	Per 100,000	No.	Per 100,000	No.	Per 100,000
Australia ..	159	2.1	173	2.2	181	2.3
Austria ..	189	2.7	216	3.1	132	1.9
Belgium ..	494	5.8	529	6.1	450	5.2
Canada ..	148	1.2	175	1.4	169	1.2
Egypt ..	143	2.1	123	1.6	66	0.8
Eire ..	257	8.6	199	6.6	233	7.8
England and Wales ..	1,534	3.6	1,463	3.4	1,586	3.6
France ..	370	0.9	341	0.8	391	0.9
Germany ..	1,185	2.5	1,225	2.6	1,498	3.1
Holland ..	181	1.9	196	2.0	200	2.0
Italy ..	695	1.5	604	1.3	703	1.5
Japan ..	1,699	2.2	1,243	1.5	1,286	1.6
Northern Ireland	61	4.5	56	3.7	63	3.6
Scotland ..	98	1.9	166	2.1	72	1.4
Spain ..	388	1.4	485	1.7	480	1.7
United States of America ..	1,808	1.3	1,847	1.3	1,830	1.3

III. AREA AND POPULATION OF PRESENT  
SURVEY

The West Penwith Peninsula (Fig. 1, overleaf) was chosen because it has a population of something over 40,000 within clearly-defined boundaries, assuming a prevalence rate of 5 per 1,000 adult population (Stocks, 1949; Logan, 1953) the area should contain some 150 cases of rheumatoid arthritis. The area comprises four local authorities (populations in brackets): Penzance Borough (20,626); St. Ives Borough (9,051); St. Just Urban District (4,125); West Penwith Rural District, less the parishes of Hayle, Phillack, Gwinear, St. Erth, St. Hilary, and Perranuthnoe (9,101). (Total: 42,903.)

*Age Structure.*—Table IV (overleaf) shows the age structure of this population, with percentage figures for England and Wales for comparison; 40.5 per cent. of the population are over the age of 45 years, compared with 34.9 per cent. of the population of England and Wales. This is only partly due to the influx of retired people; the chief reason is the emigration of younger men and women to find work elsewhere.



Fig. 1.—Area of survey.

TABLE IV  
WEST PENWITH—AGE STRUCTURE OF POPULATION  
(1951 CENSUS)

Age Group	Number (West Penwith)	Total (per cent.)	
		West Penwith	England and Wales*
0-4	3,267	7.61	8.58
5-9	2,926	6.82	7.31
10-14	2,599	6.06	6.61
15-19	2,466	5.75	6.25
20-24	2,515	5.86	6.71
25-29	2,801	6.53	7.42
30-34	2,652	6.18	7.00
35-39	3,006	7.01	7.57
40-44	3,303	7.70	7.71
45-49	3,134	7.30	7.19
50-54	2,708	6.31	6.44
55-59	2,724	6.35	5.51
60-64	2,454	5.72	4.86
65-69	2,255	5.26	4.14
70-74	1,844	4.30	3.23
75-79	1,287	3.00	2.07
80-84	610	1.44	0.99
85-89	282	0.66	0.34
90-94	59	0.14	0.08
95+	11	0.03	0.01
Total	42,903	100.0	100.0

\* 1 per cent. Sample Tables.

**Industrial Structure.**—West Penwith is the site of a very early civilization. Trading in copper and tin with the Middle East civilization was well established by 2000 B.C., and in consequence when Julius Caesar arrived in Britain, West Cornwall was populated by a vigorous and progressive race, mining the local ore, forging their own metal weapons, bartering their ingots of tin for the commodities of foreign parts, dressed in woven cloth from the East, and living in stone-built villages.

For centuries, tin-mining, fishing, and agriculture remained their staple occupations. The advent of steam power permitted a more thorough exploitation of the metal deposits, and the mid-19th century was Cornwall's most prosperous tin-mining era. In 1870 the miners numbered more than 50,000 and were producing 40 per cent. of the world's tin from 340 mines, but by 1900 the exhaustion of the more accessible lodes, combined with the advent of cheap alluvial tin from Malaya, had killed the industry. In the lean years which followed, the younger generation sought employment in the hard rock mines of West Africa and India, returning 30 or 40 years later with enough money on which to retire, but often with lungs affected by silico-tuberculosis. Today the older inhabitants include many cases of silico-tuberculosis, so that any relationship between tuberculosis and rheumatoid arthritis should be discernible.

Such is the background of the present population of West Penwith. An old civilization, proud, independent, and much intermarried. Around the coast live the fishermen of Newlyn, Mousehole, Porthcurno, Sennen, and St. Ives, while rich market gardens, that have been tilled for centuries, fill the narrow, fertile valleys that run to the South. To North and South lie the prosperous tourist centres of St. Ives and Penzance. To the West are the rocks of Land's End, and the somewhat bleak and derelict mining areas of St. Just and Pendeen. The detailed industrial structure (*cf.* Central Statistical Office, 1948) is given in Table V (opposite).

TABLE V  
WEST PENWITH—INDUSTRIAL STRUCTURE, 1955

Class		No.
Ia	Agriculture .. .. .	1,665
Ib	Fishing .. .. .	279
II	Mining .. .. .	469
III	Mining Products .. .. .	46
IV	Chemicals .. .. .	12
V	Metal Manufacturers .. .. .	1
VI	Engineering and Shipbuilding .. .. .	146
VII	Vehicles .. .. .	293
VIII	Metal Goods .. .. .	41
IX	Precision Instruments .. .. .	52
X	Textiles .. .. .	40
XI	Leather .. .. .	—
XII	Clothing .. .. .	119
XIII	Food and Drink .. .. .	259
XIV	Wood and Ash .. .. .	58
XV	Paper and Printing .. .. .	59
XVI	Other Manufactured Goods .. .. .	255
XVII	Building .. .. .	1,000
XVIII	Gas, Electricity, Water .. .. .	202
XIX	Transport .. .. .	1,311
*XX	Distribution .. .. .	2,194
XXI	Insurance .. .. .	128
XXII	National and Local Government .. .. .	713
XXIII	Professional .. .. .	830
XXIV	Miscellaneous Services .. .. .	1,981
XXV	Ex-Service Men .. .. .	17
	Total .. .. .	12,153

\* Includes Hotels, Cafes, etc.

## IV. CASE FINDING

After the willing help of Dr. St. John Brooks, Medical Consultant at Penzance, had been secured, an approach was made to the general practitioners at a meeting of the local Medical Society. Much assistance was obtained from the general medical practitioners and district nursing staff. Permission to visit their patients was readily granted and practitioners prepared a list of cases of rheumatoid arthritis known to them in their practices. Similar lists were obtained from the Rheumatism Clinic and the Physiotherapy Department at Penzance Hospital, and from the District Nurses. In this way, 262 names were obtained (Table VI).

**Controls.**—As the survey included the investigation of certain epidemiological factors, suitable controls had also to be included.

The Executive Council records contain the date of

TABLE VI  
SOURCES OF REPUTED CASES OF RHEUMATOID ARTHRITIS

Source	No. of Cases	Percentage of Total
Doctors .. .. .	97	37
Nurses .. .. .	104	40
Physiotherapy Unit .. .. .	13	5
Other .. .. .	48	18
Total .. .. .	262	100

birth and are indexed both alphabetically and by doctors. I was thus able to select a random control for each patient from the same doctor's list, matched as regards sex, age, and area of residence.

## V. DIAGNOSTIC CRITERIA

Working in the Rhondda Fach, Miall (1955) used the following criteria:

- (1) Characteristic history of polyarthritis involving peripheral joints, whether residual physical signs were present or not;
- (2) Either (a) Radiological evidence of rheumatoid arthritis in hands or feet,

Or (b) A positive differential agglutination test (Rose, Ragan, Pearce, and Lipman, 1948).

When planning the present survey, I decided that, in a scattered rural community with indifferent bus services, it would be unrealistic to expect patients to travel some 10-15 miles to Penzance Hospital for an x-ray examination and sheep cell agglutination test; I therefore based the diagnosis on the patient's medical history and a clinical examination. Remark- ing on the difficulty of diagnosis, Kellgren and Lawrence (1956) state:

"For practical purposes there appears to be a useful clinical dividing line at 'Typical rheumatoid arthritis of moderate or great severity affecting the hands and feet'."

In the present survey the patients were graded on a clinical basis similar to that suggested by Kellgren and Lawrence.

## VI. FINDINGS

(1) *Prevalence and Severity of Disability.*—With the exception of a small number of patients who were attending the Rheumatism Clinic, all the 262 cases notified were visited in their homes. After clinical examination, 95 cases were discarded\* and 167 were accepted as suffering from rheumatoid arthritis.

* The discarded cases were classified as follows:			
Osteo-arthritis .. .. .	30	Psychological condition .. .. .	4
Muscular rheumatism .. .. .	12	Nervous disease .. .. .	5
Rheumatic fever .. .. .	2	Dead .. .. .	7
Polyarthritis, not thought to be rheumatoid .. .. .	5	Left district .. .. .	7
Traumatic condition .. .. .	8	Refused examination .. .. .	1
Spondylitis .. .. .	3	Outside area of survey .. .. .	7
		Unclassified .. .. .	4



The patients with rheumatoid arthritis were then classified according to the severity of their symptoms (Table VII).

TABLE VII  
CLASSIFICATION OF 167 PATIENTS ACCEPTED AS  
CASES OF RHEUMATOID ARTHRITIS, BY SEX

Group	Clinical Assessment	Male	Female	Total
1	Probable, but doubtful ..	3	14	17
2	Definite, but mild ..	7	52	59
3	Moderately severe ..	13	48	61
4	Severe ..	2	28	30
Total .. ..		25	142	167

The diagnosis in Group 1 is open to doubt pending confirmation by x-ray examination, and these seventeen cases were therefore omitted from further analysis, bringing the numbers down to a total of 150 definite cases.

Patients included in Group 3 may be defined as "housebound", *i.e.* able to get around a little in the house and even to do light jobs, but unable to go out shopping, etc., without assistance.

Patients included in Group 4 are virtually "bed-bound", although a few manage to sit in a bedroom chair for a few hours each day. The plight of many of these Group 4 patients is pathetic. An analysis of home circumstances shows four to be well cared for in long-stay geriatric annexes, two in the Cheshire Home, and a further two in nursing homes. Most of the remaining 21 are looked after by devoted relations or friends, to whom the patients know themselves to be burdens. A few, fighting to the

last to maintain their independence, live entirely alone, relying on good neighbours (who still exist in country districts) to give them their meals, and on the District Nurse to wash them; one of them has been bedridden for 15 years. Such patients receive official material help in the form of wheel chairs, Dunlopillo mattresses, and other aids to nursing which are of great value, but more active help from voluntary organizations, in the form of regular visiting is much to be desired.

Table VIII shows that the prevalence rate of definite, clinical rheumatoid arthritis is 4.4 per 1,000. A break-down into local authority areas gives very similar figures considering the small numbers involved, indicating that the area has been evenly covered and that there is no special circumstance in any one area tending to vary the prevalence.

This rate may be compared with the figure of 4.9 per 1,000 given in the Ministry of Health Social Surveys (Stocks, 1949), and that of 5.2 per 1,000 obtained from the examination of general practitioners' records by Logan (1953). Stocks' figures are based on self diagnosis of the community investigated, and Logan's on a survey of patients' National Health Service medical cards; in consequence, both are liable to include mild forms of rheumatoid arthritis excluded from the present survey.

(2) *Age of Patients.*—An analysis of the age groups of the 150 patients is shown in Table IX and in Fig. 2 (opposite). The curve is fairly smooth and rises to a peak in the 45-54 age group.

TABLE VIII  
PREVALENCE OF RHEUMATOID ARTHRITIS, BY SEX, IN WEST PENWITH

Local Authority Area	Population aged 16 and Over			Cases of Rheumatoid Arthritis Groups 2, 3, and 4			Prevalence Rate per 1,000		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Penzance .. ..	7,371	8,834	16,205	9	56	65	1.2	6.2	3.9
St. Ives .. ..	3,013	4,221	7,234	3	27	30	1.0	6.1	4.0
St. Just .. ..	1,416	1,749	3,165	4	12	16	2.8	6.8	5.1
West Penwith .. ..	3,265	3,751	7,016	6	33	39	1.8	8.7	5.5
Total .. ..	15,065	18,555	33,620	22	128	150	1.4	6.7	4.4

TABLE IX  
AGE AT ONSET OF RHEUMATOID ARTHRITIS IN 150 PATIENTS

Age Group	Age at Onset				Population at Risk			Prevalence Rate per 1,000		
	Male	Female	Total	Per cent. of Total	Male	Female	Total	Male	Female	Total
15-24	2	12	14	10	2,115	1,375	4,490	0.96	8.7	3.1
25-34	1	23	24	16	2,597	2,856	5,453	0.38	7.9	4.4
35-44	5	26	31	21	3,021	3,288	6,309	1.6	7.9	4.9
45-54	6	31	37	24	2,641	3,201	5,842	2.3	9.7	6.3
55-64	5	21	26	17	2,153	3,024	5,178	2.3	6.9	5.2
65+	3	15	18	12	2,538	3,810	6,348	1.2	3.9	2.8
Total ..	22	128	150	100	15,065	18,555	33,620	1.4	6.9	4.4

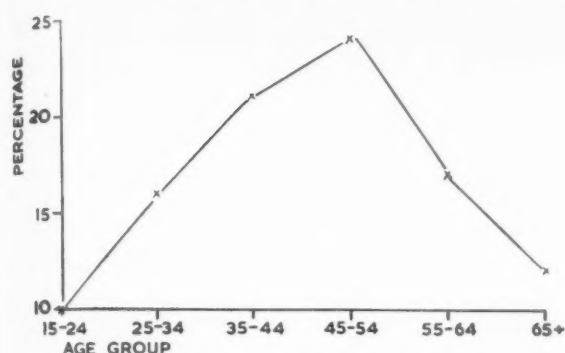


Fig. 2.—Age at onset of rheumatoid arthritis, shown as a percentage of the total by age group, in 150 cases, in Groups II, III, and IV.

This age distribution is very similar to that given by Fletcher and Lewis-Faning (1945); in an analysis of 254 patients with rheumatoid arthritis, they found the average age at onset to be 49 years in men and 48 years in women. If the present series is broken down into the same age groups as those used by Fletcher and Lewis-Faning, the following comparison can be made (Table X).

TABLE X  
PERCENTAGE AGE AT ONSET

Age Group	Fletcher and Lewis-Faning (1945)	Present Survey
Under 20	1.3	5.4
20-30	12.6	14.8
31-40	18.1	14.8
41-50	20.5	26.2
51-60	28.7	20.8
61-70	18.8	16.2

The mean age in the Empire Rheumatism Council Survey was 41 years, but this may be due in part to the fact that the patients were largely hospital cases. As will be shown later, the more acute cases tend to occur in the lower age groups and such cases are likely to obtain hospital beds. 70 per cent. of the Empire Rheumatism Council patients were aged between 25 and 54 years. In the present series, 64 per cent. come into this age group.

A larger proportion of the more severe cases in the present series were found to have started the disease at a comparatively early age. Fig. 3 shows the age at onset of Group 2 cases plotted against that of Groups 3 and 4.

(3) **Sex Ratio.**—In the present series, 22 patients were men and 128 were women, a ratio of 1 to 5.5 (corrected for sex distribution of the population). This is a higher proportion of women than has been recorded in recent surveys, but the other surveys have been carried out on hospital patients and in specialized industries.

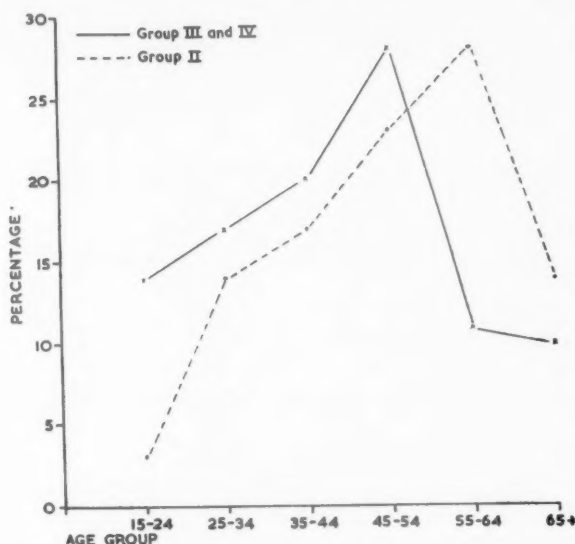


Fig. 3.—Age at onset of rheumatoid arthritis, shown as a percentage of the total, in Group II, and Groups III and IV combined.

Higher ratios are recorded by earlier writers: Fox and Van Breemen (1934) found that "A large majority of the patients are women, variously estimated at 1 to 7 or 9"; the figures given by the Ministry of Health (1924) were as high as 1 : 8 in the older age groups. In the present series the disparity between the sexes is greatest in the lower age groups, a point noted by Copeman (1955).

In the present series the onset occurred before the age of 35 in only 14 per cent. of the men as compared with 27 per cent. of the women.

A summary of previous findings on the sex ratio is given in Table XI.

TABLE XI  
SEX RATIO

Year	Author	Size of Sample	Ratio Men/Women
1924	Ministry of Health .. ..	180 (16-24 yrs)	1 : 2
1934	Fox and Van Breemen .. ..		1 : 7 or 9
1945	Fletcher .. ..	352	1 : 1.62
1949	Stocks .. ..	463	1 : 2.5
1950	Empire Rheumatism Council	532	1 : 1.62
1950	Edinburgh (quoted by Empire Rheumatism Council) ..	400	1 : 3.48
1952	Lawrence and Aitken Swan	179	1 : 3.2
1953	Logan .. ..	111	1 : 2.8

(4) **Heredity.**—A family history of rheumatoid arthritis was obtained very frequently. 35 per cent. of cases claimed to have a near relative with the

TABLE XII  
CASES OF RHEUMATOID ARTHRITIS IN NEAR RELATIVES (CLINICAL DIAGNOSIS)

Series		No. in Series	Relationship								No. of Families Involved	No. of Relatives Affected	
			Father	Mother	Brother		Sister		Sibling				
					No.	Cases of Rheuma- toid Arthritis	No.	Cases of Rheuma- toid Arthritis	No.	Cases of Rheuma- toid Arthritis			
Patients with Rheumatoid Arthritis	Men	21	1 0	0	144	1	1	136	1	280	12 (4.3%)	101	17 (17%)
	Women	113											
Controls	Men	21	0	0	209	0	0	211	0	420	2 (1%)	110	3 (2.7%)
	Women	110											

Significant ( $14.3 \pm 4.1$ ).

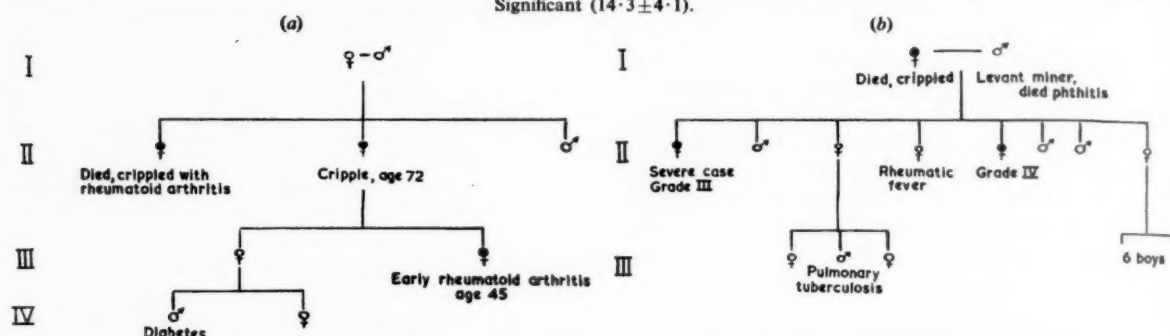


Fig. 4.—Two typical pedigrees of affected families: (a) a professional family in St. Ives, (b) a tin-mining family in St. Just.

disease, as against 3 per cent. of controls. Many of these near relatives were dead or had left the district and could not be traced, and the findings in Table XII have therefore been limited to second cases amongst near relatives which could be confirmed by visiting or by hospital notes.

In the 113 index cases, rheumatoid arthritis was confirmed in 3.5 per cent. of mothers and 6.1 per cent. of sisters; siblings gave an incidence of 4.3 per cent. Second cases occurred in 17 per cent. of the 101 families included in this inquiry, as compared with 2.7 per cent. of control families, a finding which is statistically significant ( $14.3 \pm 4.1$ ). Two typical pedigrees are shown in Fig. 4.

These results correspond with those of Miall (1955), who, using a similar strict clinical diagnosis of rheumatoid arthritis in near relatives, found that 4.1 per cent. of siblings were affected.

A summary of the findings of previous surveys on the heredity factor in rheumatoid arthritis is given in Table XIII (opposite).

#### (5) Association with Endocrine Dysfunction

(a) *Thyroid Gland*.—A note was made of thyroid dysfunction amongst patients and their near relatives, and amongst controls. No significant difference was found (Table XIV, opposite).

(b) *Diabetes*.—Patients, controls, and near relatives were likewise questioned concerning diabetes. No significant difference was found (Table XIV).

(6) *Factors affecting Female Patients*.—Ninety-three women with Grade II, III, or IV rheumatoid arthritis, who were able to give a reliable record of their menstrual history, were considered under this head, and were compared with 92 controls.

(a) *Marital State*.—Twenty-eight were spinsters, and the 65 married women had had between them 110 children. Of the 92 controls, nine were spinsters, and the 83 married women had had between them 171 children.

(b) *Menopause*.—Rheumatic symptoms were first noted within a year before or after the termination of menstruation in 21 patients (22.5 per cent.) and within 2 years of its termination in a further ten patients (9.5 per cent.).

Fletcher and Lewis-Faning (1945), in a survey of 206 women patients, found that the disease was associated with the menopause in twenty cases (9.6 per cent.).

In the Empire Rheumatism Council's survey of 111 patients who had reached the menopause (Lewis-Faning, 1950), the disease had started within a year

TABLE XIII  
RHEUMATOID ARTHRITIS IN NEAR RELATIVES—SUMMARY OF PREVIOUS INQUIRIES

Year	Author	Size of Sample of Rheumatoid Arthritis Cases	Parents Affected		Siblings Affected		Second Case in Family (Per cent.)
			Father (Per cent.)	Mother (Per cent.)	Total	Per cent. Affected	
1928	Ministry of Health	180					42
1928	Strangeways ( <i>quoted in Ministry of Health Report</i> )	200					56
1947	Fletcher	254					4.7
1950	Empire Rheumatism Council	532 Cases 532 Controls	7 3	15 9	2,151 2,143	3.8 1.8	
1952	Barter	100 Cases 100 Controls					5.3
1955	Miall	59 Cases 89 Controls		1 2	244 334	4.1 —	
1956	Present Survey (see Table XII)	113 Cases 110 Controls	0.9 —	3.5 1	280 420	4.3 1	17 2.7

TABLE XIV  
THYROID DYSFUNCTION AND DIABETES IN PATIENTS, CONTROLS, AND NEAR RELATIVES

Series		Total	Thyroid Dysfunction		Diabetes	
			No.	Per cent.*	No.	Per cent.*
Patients .. .. .		113	8	7	—	—
Controls .. .. .		110	3	2.7	2	0.5
Parents	Patients .. .. .	226	1	0.45	6	2.6
	Controls .. .. .	214	1	0.46	3	1.4
Siblings	Patients .. .. .	280	3	1.1	4	1.4
	Controls .. .. .	343	4	1.2	4	1.1

\* Not significant.

of the termination of menstruation in 24 per cent. of cases, a finding very similar to that in the present series.

(c) *Menstruation*.—Thirty-seven women patients who had developed rheumatoid arthritis before the menopause were questioned to ascertain whether menstruation had any effect on the severity of the rheumatic symptoms. Thirty-one stated that menstruation had no effect, three stated that their joints were worse, and three claimed some alleviation of symptoms during menstruation.

When menstruation had an adverse effect, this was noted for 24-48 hours before the menstrual flow; two of the three patients concerned stated that the symptoms were alleviated once menstruation had started.

(d) *Pregnancy*.—Ten patients who were under 70 years of age at the time of the interview had borne children after the onset of rheumatoid arthritis (eleven pregnancies). In one confinement, rheumatic symptoms had not been materially affected, but the symptoms had been definitely, and

in many cases dramatically, relieved in the other ten confinements, although the rheumatic pains invariably returned 2 to 3 months after delivery.

In the Empire Rheumatism Council's survey (Lewis-Faning, 1950), 21 out of 22 patients who became pregnant after the onset of rheumatoid arthritis, had improved during pregnancy, but seventeen of them had become worse again after parturition.

(7) *Association of Rheumatic Fever*.—Spender and Garrod (1897) described a form of rheumatoid arthritis which followed attacks of rheumatic fever. The differential diagnosis may be very difficult, particularly when in rheumatic fever the inflammation invades the small joints of the hands. Three such cases were cited by Fletcher and Lewis-Faning (1945).

One such case which occurred in West Penwith is of sufficient interest to record:

A blacksmith, aged 38, had had at the age of 17 a classical attack of rheumatic fever, and had been kept in bed by his doctor for 6 weeks. Most of the larger



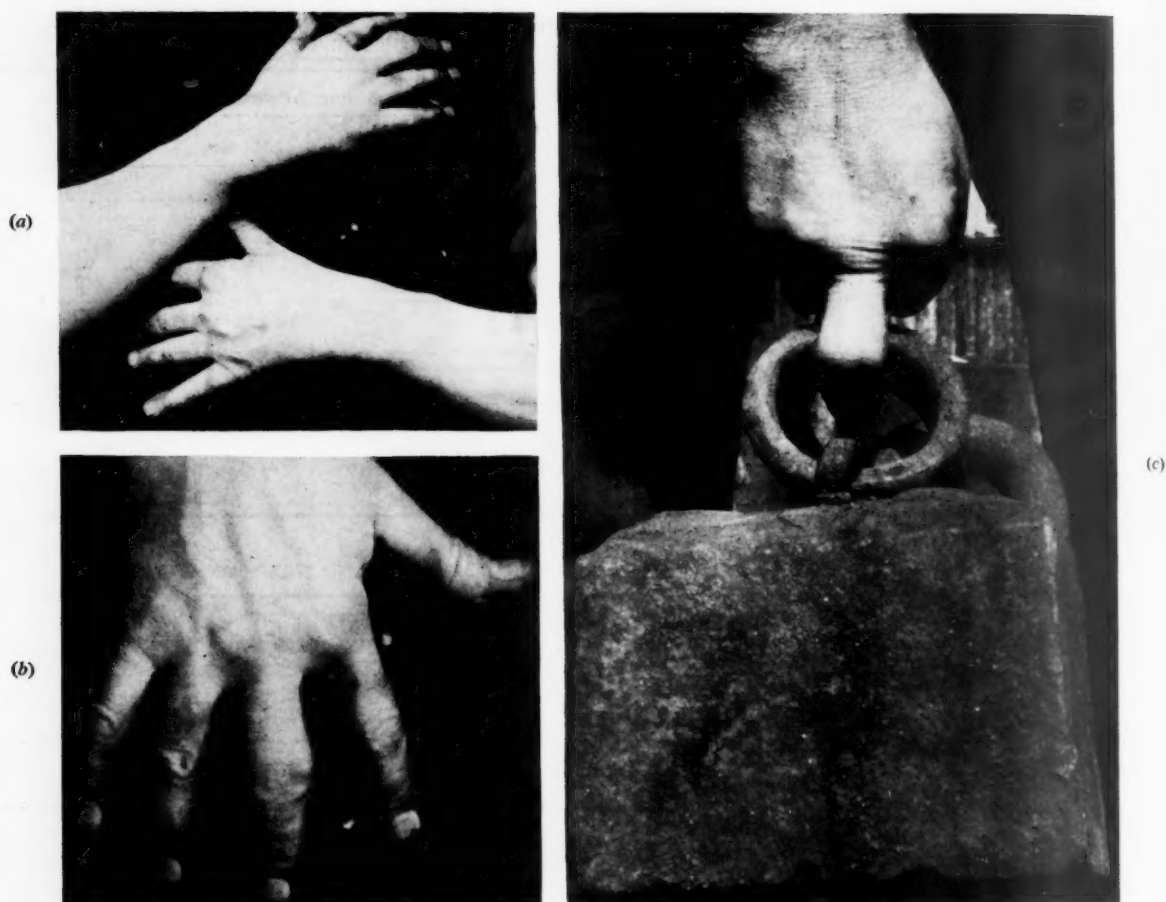


Fig. 5(a-c).—Enlarged finger joints in a blacksmith aged 38 who developed rheumatoid arthritis after an attack of rheumatic fever at the age of 17.

joints in his limbs were affected in succession, but the condition gradually subsided under treatment with salicylates, and the patient was able to return to work. Two years later, pain and swelling returned to the ankles, elbows, wrists, and phalanges. These pains have never left him, but the patient has managed to continue working.

Some of the phalangeal joints are grossly enlarged, and a few years ago a surgeon suggested amputating one of the swollen fingers. The patient now takes pride in showing how he can lift 56 lb. with a finger which might have been amputated (Fig. 5a-c).

A diagnosis of arthritis following rheumatic fever was made, but this case is further complicated by the fact that the elder brother, who is 44 years old and also a blacksmith, also has moderately severe rheumatoid arthritis (Fig. 6a and b, opposite).

Table XV shows the number of patients who gave a history of rheumatic fever in childhood or immediately before the onset of rheumatoid arth-

ritis. These amounted to 9.7 per cent. as against 7.3 per cent. of the controls. Only those with a definite history of a prolonged period in bed with rheumatic fever are included. An equal number of patients also gave somewhat indefinite histories of "growing" pains.

TABLE XV  
RHEUMATIC FEVER IN PATIENTS AND CONTROLS,  
BY SEX  
(PATIENTS UNDER 70 YEARS OF AGE)

Series	Sex	Size of Sample	History of Rheumatic Fever	
			No.	Per cent.*
Patients	Men	21	2	9.5
	Women	92	9	9.8
	Total ..	113	11	9.7
Controls	Men	21	—	—
	Women	89	6	6.7
	Total ..	110	6	7.3

\* Not significant  $1.3 \pm 4.0$ .



Fig. 6(a and b).—Finger joints of a blacksmith aged 44, elder brother of the above, who had developed moderately severe rheumatoid arthritis but had not had rheumatic fever.

No support for the association of rheumatic fever and rheumatoid arthritis can be drawn from the present small series.

Glover (1928) found a history of rheumatic fever in 20 per cent. of men and 18 per cent. of women rheumatoid arthritis patients, but rheumatic fever was a far more common disease in the early 1920s. Fletcher and Lewis-Faning (1945), in a survey of 254 rheumatoid arthritis patients, found only ten (4 per cent.) who had had rheumatic fever.

If rheumatic fever were truly a predisposing cause of rheumatoid arthritis, one might expect to see some reduction in the incidence of rheumatoid arthritis following on the reduced numbers of cases of rheumatic fever, but Table II seems to show that rheumatoid arthritis is tending to become more rather than less common. The sex ratio is also against any clear association, rheumatic fever being rather more common in males.

(8) **Association with Pulmonary Tuberculosis.**—Miall (1955) found an association between pulmonary tuberculosis and rheumatoid arthritis in his x-ray survey of a Welsh mining community. A history of pulmonary tuberculosis was twice as frequent amongst rheumatoid arthritis patients as amongst controls in the present series, but, owing to the small numbers of patients, the findings were not significant (Table XVI).

#### (9) Predisposing Factors

(a) **Trauma.**—In the past this has often been cited as a cause of rheumatoid arthritis (Spender

TABLE XVI  
PULMONARY TUBERCULOSIS IN PATIENTS, CONTROLS,  
AND NEAR RELATIVES

Series		Total	History of Pulmonary Tuberculosis	
			No.	Per cent.*
Subjects	Patients ..	113	9	8
	Controls ..	110	4	3.7
Parents	Patients ..	226	7	3.1
	Controls ..	214	7	3.2
Siblings	Patients ..	280	8	2.8
	Controls ..	343	8	2.3

\* Not significant.

and Garrod, 1897), but more recent opinion suggests that, although trauma may well decide the joints affected by osteo-arthritis, it is not an aetiological factor in rheumatoid arthritis. In the present survey, trauma had occurred on only four occasions within a year of the onset of rheumatoid arthritis.

(b) **Psychological Stress and Strain.**—The collection and evaluation of evidence regarding psychological factors was difficult, in that intimate details of family life are not readily imparted to a comparative stranger, and the results shown in Table XVII (overleaf) may underestimate the importance of stress. On the other hand, a rheumatic patient is more likely than a control to remember emotional incidents which might be connected with his illness.

TABLE XVII  
PSYCHOLOGICAL STRESS AND STRAIN, BY SEX  
(PATIENTS UNDER 70 YEARS OF AGE)

Series	Sex	Size of Sample	Psychological Factor (within 2 yrs of onset)		
			Unconnected	Possible	Probable
Patients	Men	21	15	3	3
	Women	93	36	31	26
	Total ..	113	55	29	29 (25 per cent.)*
Controls	Men	21	17	2	2
	Women	86	72	7	7
	Total ..	107	89	9	9 (8.4 per cent.)*

\* Statistically significant:  $20 \pm 4.2$ .

Examples of the types of stress to which these patients had been subjected are given below:

(i) *Domestic Unhappiness (11 cases).*—One woman aged 65 had led a very hard life. Her husband deserted her when her second son was 4 years old, and arthritis started at about this time. One son had since died of spinal trouble, and the second was under treatment for cancer of the lung.

(ii) *Tragic or Sudden Death (10 cases).*—One woman aged 38 had married at the age of 25. She had always been scared of childbirth, and when first married went to live with her married sister, who died in childbirth only 2 months later. The patient took to her bed with rheumatoid arthritis the following month, and has now been bedridden for 13 years.

(iii) *Worry—Business, Financial, and Family (4 cases).*

(iv) *Trouble arising from the War (3 cases).*

(v) *Retirement from Business (2 cases).*

Previous writers differ on the importance to be attached to psychological factors in the aetiology of rheumatoid arthritis. Glover (1928) stated that all writers were agreed that the onset of rheumatoid arthritis could often be traced to mental stress, sudden shock, continuous anxiety over relatives, domestic unhappiness, and financial worry. Bach (1935) stated that an unusual number of women patients attributed their symptoms to their experiences while doing war work in France or to the emotional strain caused by the death of a fiancé at the front. Gordon (1939) remarked on the changes in circulation, secretory glands, and plain muscle that can be brought about by over-activity of the autonomic nervous system. He found that the onset of disease followed emotional crises in 28 per cent. of fifty patients. Fletcher (1947) remarked that psychological factors were "particularly noticeable in the London 'blitz' of 1940-41 and again

when the flying bombs and rockets commenced to arrive. Not only were cases arising *de novo*, as a result of these stresses, but old cases became reactivated". He quoted an analysis (previously unpublished) of 27 per cent. of a series of 200 cases of rheumatoid arthritis in which precipitating emotional factors were present (p. 129):

Long-continued illness of a relative ..	8
Air-raid incidents .. .. .	12
Financial and business worries ..	14
Domestic unhappiness .. .. .	12
Worry over the fate of a relative in the war ..	6
Fear of an expensive law suit and its consequences .. .. .	2

On the other hand, the Empire Rheumatism Council (Lewis-Fanning, 1950), in a survey of 500 cases, could find no significant difference in the degree of stress to which patients and controls had been subjected.

## VII. COMMENTARY

(1) *Data.*—The method of collecting data from general practitioners, nurses, and clinics worked smoothly but was not 100 per cent. complete; for instance, two further cases were discovered when questioning control subjects concerning their family history.

The controls were selected from the Executive Council Register of patients on doctors' lists. The method proved laborious in that the Register was by no means up to date, and contained many names of persons who had left the district, moved house, or died. In future it may be possible to obtain the help of the Ministry of Health Social Survey team, who might note the required information in the course of their routine visits.

(2) *Prevalence.*—The prevalence rates and sex ratio in West Penwith correspond reasonably closely with the findings of previous surveys.

(3) *Heredity.*—In considering heredity, it is important to decide whether to accept a history suggestive of rheumatoid arthritis in a near relative or to demand a clinical diagnosis, thus excluding all relatives who have died or are too far off to be investigated. Using the first method, the present survey shows a family history of rheumatoid arthritis in 35 per cent. of cases (compare Glover, 1928: 40 per cent. family history), but using the second method it was possible to confirm diagnosis by clinical examination or hospital notes in only 17 per cent. of cases.

(4) *Aetiology.*—No obvious association, positive or negative, was found between diabetes and rheu-



matoid arthritis, though superficially the two conditions have aetiological points in common, both being diseases of middle life, frequently associated with the menopause, and having a sex ratio of approximately 1:3.

An interesting finding was the apparent association between the activity of the female sex glands and rheumatoid arthritis. The number of children tended to be larger in control families (two children per family) and spinsters were more numerous amongst the women patients. Almost one-third of the women patients developed the first symptoms of arthritis within 2 years of the termination of menstruation. In ten of eleven cases in which the disease began in the child-bearing years and pregnancy followed, there was a spectacular alleviation of rheumatoid symptoms during pregnancy.

The importance of psychological factors in the aetiology of rheumatoid arthritis has been under discussion ever since the disease was first described as a separate entity by Garrod (1858). The part played by stress is difficult to determine, and expert evidence is much divided, but the present survey suggests that stress plays an important part in the medical history of persons susceptible to rheumatoid arthritis.

Information concerning occupation, susceptibility to allergic states, and skin conditions was collected; the figures are too small to have significance, but are available for inclusion with other surveys. Only one case of psoriasis was encountered amongst the 150 patients with rheumatoid arthritis, whereas two cases were recorded in the control series.

**(5) Disability.**—The severity of the disease varied widely and it is difficult to understand why some cases remain static for many years in a comparatively mild state whilst others rapidly progress to crippling. In all degrees of severity, however, it seems that the disease burns itself out, a course compatible with the influence of an adverse psychological background with which the patient finally comes to terms.

Whatever the cause of the final arrest, the physician must always work to this end, and ensure that the joints are maintained in a good functional position in the hope of eventual improvement.

#### SUMMARY

A survey of the prevalence of rheumatoid arthritis has been carried out in a circumscribed area of West Cornwall with a population of 42,903.

Some 260 patients, of whom 167 were diagnosed as cases of rheumatoid arthritis, were visited in their homes, together with an equal number of matched controls.

The rheumatoid arthritis patients were classified according to severity, in four grades. Grade I patients were those in which the diagnosis could not be accepted without confirmatory x-ray examination, and, as this was not available in the field, they were excluded from further analysis.

There were 150 patients with definite clinical rheumatoid arthritis (Grades II, III, and IV) giving a prevalence rate of 4.1 per thousand, with a sex ratio of 1 to 5.5. The maximum onset occurred in the 45-54 age group, but there was a tendency for the more severe cases to develop the disease at an earlier age.

The influence of heredity in the series was significant, 17 per cent. of patients having second cases amongst parents and siblings, compared with 2.7 per cent. of controls ( $14.3 \pm 4.1$ ). Only second cases confirmed by clinical examination or hospital notes were included.

No significant difference was found in the prevalence of thyroid or pancreatic dysfunction.

The findings suggest that the female sex glands play some part in the aetiology; in women patients, the onset of rheumatoid arthritis occurred within one year of the termination of the menopause in 22.5 per cent. of cases, and within 2 years in almost one-third. Pregnancy, which occurred on eleven occasions after the onset of rheumatoid arthritis, resulted in a marked but transient relief of rheumatic symptoms in nine of the ten patients concerned. There was an undue proportion of spinsters amongst rheumatoid arthritis patients, and, amongst the married women, the size of children was smaller than in the control series.

Rheumatic fever was not found more frequently in the past history of the rheumatoid arthritis patients than in that of the controls, although in one or two instances rheumatoid arthritis followed closely after attacks of rheumatic fever.

Pulmonary tuberculosis was found approximately twice as frequently in the patients as in the controls, but the size of the sample is too small for this finding to be statistically significant.

Physical trauma to the joints was of no aetiological importance, but psychological stress or strain within 2 years of the onset of rheumatoid arthritis occurred in 25 per cent. of patients as against 8.4 per cent. of controls (difference  $16.6 \pm 5.4$ ).

I should like to thank the Empire Rheumatism Council, a grant from whom has made this work possible, Dr. St. John Brooks, consultant physician at Penzance, and the general practitioners in the area, for their willing co-operation; Miss P. E. Coleman for the photographs shown in Figs 5 and 6, and the district nurses, particularly



Miss E. H. Penhaul and Miss W. M. Pellow, who did so much in discovering the cases.

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### Enquête sur l'arthrite rhumatismale en Cornouailles de l'Ouest

(Compte-rendu à l'Empire Rheumatism Council)

## RÉSUMÉ

On a effectué une enquête sur la fréquence de l'arthrite rhumatismale dans une partie circonscrite de Cornouailles de l'Ouest, avec une population de 42.903.

Près de 260 sujets, dont 167 diagnostiqués comme cas d'arthrite rhumatismale, ainsi qu'un nombre égal de témoins assortis, furent visités à leur domicile.

Ceux atteints d'arthrite rhumatismale furent classés, selon la sévérité, en quatre grades. Dans le Grade I se trouvèrent ceux chez qui on ne pouvait pas accepter le diagnostic sans une confirmation radiologique, et comme les circonstances ne s'y prêtaient pas, on les exclut de toute analyse ultérieure.

Il y avait 150 malades avec une arthrite rhumatismale cliniquement définie (Grades II, III et IV) donnant une fréquence de 4,1 par mille, les sexes étant en proportion de 1 à 5,5. Le début de la maladie était le plus fréquent à l'âge de 45 à 54 ans, mais on nota la tendance des cas plus sévères à débiter à un âge plus jeune.

L'influence de l'hérédité dans cette série fut significative, 17% des malades ayant un parent, un frère ou

une sœur atteints, tandis que pour les témoins l'atteinte familiale ne se voyait que chez 2,7% ( $14,3 \pm 4,1$ ). Ces pourcentages d'atteinte familiale comprennent seulement des cas confirmés par un examen clinique ou par un dossier d'hôpital.

On ne trouva pas de différence significative dans la fréquence des troubles thyroïdiens ou pancréatiques.

Les résultats suggèrent que les glandes sexuelles de la femme jouent un rôle étiologique; l'arthrite rhumatismale débuta chez 22,5% des femmes au cours de l'année qui suivit la ménopause et chez presque un tiers avant que deux ans se soient écoulés. La grossesse survenant après le début de l'arthrite rhumatismale apporta un soulagement marqué, bien qu'éphémère, à neuf sur dix malades. Il y avait une forte proportion de vieilles filles parmi les atteintes d'arthrite rhumatismale, et parmi les mariées le nombre d'enfants des malades était inférieur à celui des témoins.

Les antécédents personnels de rhumatisme articulaire aigu ne furent pas plus fréquents chez les malades que chez les témoins, bien que dans un ou deux cas la maladie chronique succéda rapidement à l'aiguë.

On trouva de la tuberculose pulmonaire presque deux fois plus souvent chez les rhumatisants que chez les témoins, mais la série n'est pas assez grande pour que ce fait soit statistiquement significatif.

Le traumatisme articulaire fut sans importance étiologique, mais la fatigue et la tension psychologique au cours des deux ans précédant le début de l'arthrite rhumatismale survinrent chez 25% des malades et seulement chez 8,4% des témoins (différence  $16,6 \pm 5,4$ ).

### Estudio de la artritis reumatoide en Cornualla Occidental

(Informe para el Empire Rheumatism Council)

## SUMARIO

Se estudió la incidencia de la artritis reumatoide en una región circunscrita de Cornualla Occidental, con una población de 42.903.

Cerca de 260 sujetos, 167 de ellos diagnosticados como casos de artritis reumatoide, así como un número igual de testigos apareados, fueron visitados en sus casas.

Los sujetos con artritis reumatoide fueron clasificados, según la severidad, en cuatro grados. En el Grado I se colocaron aquellos en que el diagnóstico no se pudo aceptar sin confirmación radiológica, a no ser esto posible en las condiciones del estudio, todos fueron excluidos del analisis ulterior.

Hubo 150 enfermos con artritis reumatoide clínicamente definida (Grados II, III y IV) dando una incidencia de un 4,1 por mil y una proporción de sexos de 1 a 5,5. El comienzo de la enfermedad fué más frecuente a la edad de 45 a 54 años, pero se notó la tendencia a un empuje más temprano de los casos más graves.

La influencia de la herencia en esta serie fué significativa, encontrándose un segundo caso en la familia (padre, madre, hermano o hermana) de un 17% de los enfermos y tan sólo de un 2,7% ( $14,3 \pm 4,1$ ) de los testigos. Se incluyen aquí solamente segundos casos confirmados por un examen clínico o por fichas hospitalarias.

No hubo diferencia significativa en la incidencia de los disturbios tiroideos y pancreáticos.

Los datos sugieren que las glándulas sexuales de la mujer desempeñan un papel etiológico: la artritis reumatoide empezó en el 22,5% de las mujeres durante el primer año que siguió el fin de la menopausia y en casi

una tercera parte de ellas dentro de dos años. El embarazo trajo un alivio marcado, aunque efímero a nueve de la diez reumáticas en que ocurrió. Hubo una fuerte proporción de solteras entre las mujeres con artritis reumatoide y las casadas reumáticas tuvieron menos hijos que las casadas sanas.

Los antecedentes personales de reumatismo poliarticular agudo no fueron más frecuentes en los enfermos que en los testigos, aunque en un o dos casos la enfermedad crónica sucedió rápidamente a la aguda.

Se vieron casi dos veces más casos de tuberculosis pulmonar entre los reumáticos que entre los testigos, pero esta serie es demasiado pequeña para que este hecho tenga un significado estadístico.

El trauma articular no tuvo importancia etiológica, pero la fatiga y la tensión psicológica en el curso de los dos años que precedieron el comienzo de la artritis reumatoide sobrevivieron en un 25% de los enfermos y sólo en un 8,4% de los testigos (diferencia de  $16,6 \pm 5,4$ ).

## SUBCUTANEOUS HAEMORRHAGES IN RHEUMATOID PATIENTS TREATED WITH PREDNISONE\*

BY

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Numerous reports have recently appeared calling attention to skin haemorrhages in patients receiving prednisone and prednisolone (Black, Yielding, and Bunim, 1957; Denko and Schroeder, 1957; Boland, 1956, 1957; Solem and Römcke, 1956; Neustadt, McClendon, Olash, and Best, 1956; Kinsell, Michaels, Coehlo, Foreman, and Friskey, 1955; Brown, 1956).

The occurrence of these ecchymotic lesions has usually been listed among the other side-effects of therapy with these newer steroid substances. Boland (1956) reported that 24 of seventy patients (34 per cent.) receiving prednisone and prednisolone developed subcutaneous haemorrhages, but the report by Denko and Schroeder (1957) is the only detailed study of this toxic manifestation to these steroids. They observed a 20 per cent. incidence of purpuric lesions in a series of 75 patients who received these drugs. Similar lesions were previously observed in patients receiving the original or older steroid preparations (cortisone, hydrocortisone, and corticotropin); however, it has been our experience that this bleeding tendency has appeared with increased frequency since the introduction of the so-called delta-1 or meta drugs. The purpose of this report is to call attention to these purpuric lesions and to summarize some studies that have been carried out in an effort to explain the mechanism of their production.

### Clinical Observations

In the past 12 months, 44 patients under treatment for rheumatoid arthritis at the Arthritis Clinic of the University of Colorado Medical Centre have been observed who developed superficial haemorrhagic

areas in the skin while receiving long-term corticosteroid therapy. During this period a total of 153 patients with rheumatoid arthritis were under active therapy, of whom 109 received prednisone. Thus, the occurrence of subcutaneous haemorrhages in 44 patients represents an incidence of 40 per cent. of this toxic reaction. In most instances these patients had previously received the older forms of steroids (cortisone and/or hydrocortisone) for periods ranging from months to years. In this group it was not until the introduction of prednisone that the increased incidence of these vascular lesions became obvious both to the patients and to the physicians responsible for their care. The daily amount of prednisone administered in this group of patients varied from 10 to 20 mg. per day in three or four equal doses.

*Haemorrhagic Lesions.*—Most commonly, the patients reported that they "just noticed" the purpuric spots on their skin. Questioning revealed that the haemorrhages frequently came on without apparent cause, but some could recall having received a minor trauma shortly before the onset of the skin changes. A number of patients observed their rapid development and witnessed a gradual spread to their maximum size within 10 to 15 minutes. These lesions were painless and associated with no other complaints. They varied in size from a few millimetres to extensive areas covering as much as half a forearm and appearing as a large ecchymosis. The smaller lesions appeared at times as a telangiectasia. A typical haemorrhagic lesion was round or oval, flat, and about 1 cm. in diameter (Fig. 1, opposite). When they appeared these areas were discrete and of a bright red colour; this deepened on the following day and slowly went through the colour changes of a bruise, finally fading completely in 10 to 15 days; only rarely did the lesions remain longer as pigmented patches of a brownish-tan colour. If the skin overlying a few

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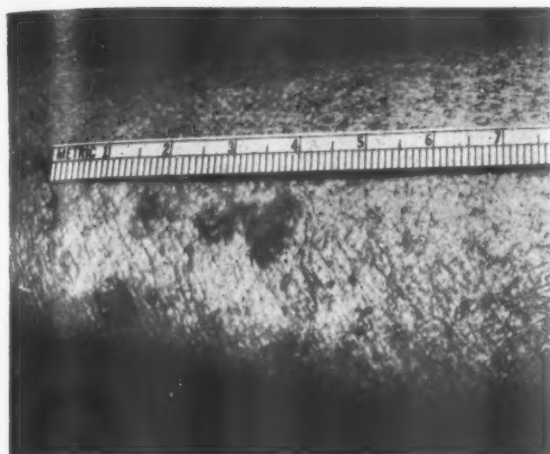


Fig. 1.—Skin of forearm showing several small and one large haemorrhagic area, the largest measuring 1.5 cm.

of the recently developed spots was broken by some minor injury, such as a scratch, it oozed a few drops of blood, but healed normally. In this series of patients the forearms, wrists, and dorsa of the hands and fingers were most common sites, less frequently these purpuric lesions were seen on the neck, shoulders, upper arms, and face, and a few occurred on the lower extremities. Examples of the variety of lesions observed are illustrated in Fig. 2. This distribution to the extremities, face, and neck indicates that the areas of predilection are those constantly subjected to minor trauma. When large ecchymotic areas developed a history of a direct blow or a fall was usually obtained.

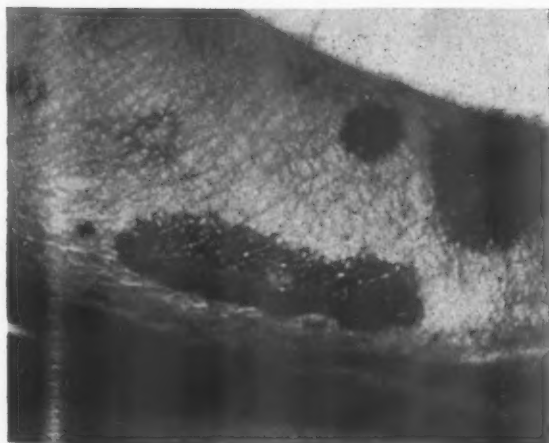
These skin manifestations were not seen in patients below the age of 30 years. In no instance was there evidence of internal haemorrhage. In a few patients prednisone was withdrawn, and in these



A



B



C



D

Fig. 2.—Four patients, A, B, C, D, showing characteristic haemorrhagic lesions in the skin of the upper extremity.



the skin lesions disappeared; in several others, the dose was reduced to 5 mg. per day, but even with this smaller amount of the hormone this haemorrhagic tendency continued.

*Production of Haemorrhagic Lesions.*—The influence of minor trauma in the formation of these lesions was easily demonstrated. In several patients with this steroid-induced bleeding tendency, lesions similar to those occurring spontaneously were produced by mechanical trauma. The injury was accomplished with minimal discomfort by the quick snapping action of a wooden spatula held close to the skin of the forearm of the subject. Within a few seconds of this blunt blow petechiae appeared in the areas of skin which had just been struck. The induced haemorrhages could be seen to reach their maximum size in a period of 15 minutes.

#### Laboratory Observations

The first eleven of these 44 subjects were selected for extensive laboratory studies, to determine, if possible, the mechanism of production of this observed phenomenon. A summary of the clinical and routine laboratory data concerning the observed haemorrhagic lesions is shown in Table I and in Table II (opposite).

The sensitized sheep erythrocyte agglutination reaction by the modified Ziff technique (Ziff, Brown, and McEwen, 1954) was positive in eight patients;

this test was not obtained in the other three patients. A preparation of the peripheral blood for L.E. cells was performed in every case, and only one was positive. The routine serologic test for syphilis (V.D.R.L.) was positive in two patients. The erythrocyte sedimentation rate (Westergren) was raised in each subject. The white blood cell count was slightly raised in each subject, averaging 12,000 cells per c.mm. The haematocrit values were within normal limits. The results of other special blood studies are summarized in Table III (opposite).

In those patients in whom the platelet count, bleeding time, coagulation time, and prothrombin time were determined, the results were within normal limits.

The capillary resistance of the skin at the elbow on the volar surface was measured by the application of a negative pressure suction cup. The instrument\* used in this test of capillary fragility permitted the application of a constant negative pressure to a measured area of skin surface. The cup was round with inner diameter 1.7 cm. A negative pressure of 20 mm. Hg was applied to the skin for exactly one minute. Using this technique, nine of the ten patients studied had no increased capillary fragility.

The capillary fragility was also tested in six of the eleven patients by the Rumpel-Leede test. The sphygmomanometer was applied to the upper arm

\* Benoit, E., Paris, France; designed by Lavoluit.

TABLE I  
PARTICULARS OF THERAPY IN ELEVEN PATIENTS

Patient No.	Sex	Age (yrs)	Duration of Rheumatoid Arthritis (yrs)	Steroid Therapy					
				Previous				Present	
				Cortisone		Hydrocortisone		Prednisone	
				Duration (yrs)	Dose (mg./day)	Duration (yrs)	Dose (mg./day)	Duration (yrs)	Dose (mg./day)
1	M	48	7	4	50-100	2	30	$\frac{1}{2}$	15
2	F	71	30	Few mths	50-100	2	40-75	$1\frac{1}{2}$	10-20
3	M	63	10	3	50-100	1	75	$1\frac{1}{2}$	15
4	F	61	6	5	25-50			$1\frac{1}{2}$	10-15
5	F	63	4	$\frac{1}{2}$	37.5-100			$\frac{1}{2}$	15-25
6	F	56	4	$1\frac{1}{2}$	37.5-100			$\frac{2}{3}$ $\frac{1}{6}$	15* 10
7	F	67	35					$1\frac{1}{2}$	10-20
8	F	56	4	3	50-100			$1\frac{1}{2}$	12 $\frac{1}{2}$
9	M	55	26	4	75-100			$\frac{5}{6}$	10-15
10	F	66	6	4	67.5			$1\frac{1}{2}$	20
11	F	37	4			1	10	1	10-20

\* Prednisolone therapy for 9 months preceding prednisone therapy.

TABLE II  
ROUTINE LABORATORY DATA

Patient No.	Sensitized Sheep Cell Agglutination Reaction	Erythrocyte Sedimentation Rate	V.D.R.L.	L E. Cells	Uric Acid	Haematocrit (per cent.)	Haemoglobin (g. per cent.)	Red Blood Cells (m./c.mm.)	White Blood Cells	Differential (per cent.)
1	Positive	42		Negative		46	13.4	4.82	8,900	77 polymorphs 21 lymphocytes 2 eosinophils
2	Positive	33	Negative	Negative	10.5 9.0 8.0 7.1	42	13.1		11,600	64 polymorphs 32 lymphocytes 3 monocytes 1 eosinophil
3	Positive	29	Negative		5.7	48	14.7	4.84	18,100	73 polymorphs 27 lymphocytes
4	Not done	12	Negative	Negative		48	16.8		10,350	63 polymorphs 31 lymphocytes 6 monocytes
5	Positive	43	Weak positive	Negative	3.8 5.0	43	14.3	4.80	5,700	52 polymorphs 45 lymphocytes 2 monocytes 1 eosinophil
6	Positive	44	Negative	Negative	2.6 5.2	45	13.9	4.92	9,000	71 polymorphs 26 lymphocytes 2 basophils 1 eosinophil
7	Positive		Positive	Positive	4.0	43	12.9	4.52	3,300	5 polymorphs 95 lymphocytes
8	Positive	43	Negative	Negative	3.4 6.4	47	15.4	5.06	15,800	77 polymorphs 23 lymphocytes
9	Not done	5		Negative	6.4	56	17.5	5.4	12,400	68 polymorphs 31 lymphocytes 1 eosinophil
10	Not done		Negative	Negative		40	13.0	4.0	5,000	
11	Positive	44	Negative	Negative	3.8 5.5	42	12.6	4.52	13,500	61 polymorphs 38 lymphocytes 1 basophil

TABLE III  
COAGULATION TESTS

Patient No.	Platelets (1,000/c.mm.)	Bleeding Time		Coagulation Time		Fragili-meter	Prothrombin	
		Min.	Sec.	Min.	Sec.		Time (sec.)	Per cent. of Normal
1	258,000						15.2	Above 110
2	282,000	1	45	4		Normal	15.8	100
3	194,000	2	25	3		Normal	16.0	100
4	218,000	1	50	3	40		15	100
5	127,000	1	50	5		Normal	16.6	100
6	224,000	1		5	30	Normal	16	100
7	230,000					Normal	14.1	120
8	287,000		45	2			14.9	Above 110
9	178,000					Normal	18.1	65
10	150,000						15.3	110
11	269,000		25	3		Normal	16.5	100

and the pressure held half-way between systolic and diastolic for 5 minutes. There was no evidence of decreased capillary resistance by this technique.

Other special coagulation investigations included the recalcification time, prothrombin consumption, thrombin time, coagulogram, and fibrinolysis.\* No significant abnormalities were found in any of these special studies.

Serum proteins, determined by the method of Jencks, Jetton, and Durum (1955), revealed a reversal of the albumin/globulin ratio in three of the nine cases studied. The electrophoretic pattern showed a decreased albumin content with an increased alpha 1 and alpha 2 globulin, a moderately elevated beta globulin, and an increased gamma globulin (Table IV). These findings are similar to those reported by Houli and Hasson (1956) in a series of patients with rheumatoid arthritis.

The blood ascorbic acid levels were measured in eight of these eleven subjects and the content was decreased in each instance. It is well known that the vitamin C levels may be low in patients with rheumatoid arthritis without steroid therapy, and this finding was therefore not unexpected.

Skin biopsies of these lesions were taken from four patients. No significant changes were observed in the routine haematoxylin and eosin stained sections which would explain the extravasation of blood.

\* These determinations were made by Dr. Kurt von Kaulla of the Coagulation Laboratory of the University of Colorado Medical Centre.

### Discussion

The occurrence of spontaneous skin haemorrhages is a classical finding in Cushing's syndrome and has been repeatedly observed in the hypercortisonism produced in patients receiving exogenous adrenocorticosteroids and adrenocorticotropin. The observed increased frequency of these purpuric spots after prednisone therapy which forms the basis of this report and the observed increased incidence noted by Black and others (1957), Denko and Schroeder (1957), and Boland (1957) would appear to be an exaggeration of this well-recognized tendency to easy bruising. When our attention was drawn to this undesirable side-effect, a search was made of the literature to determine what factors might have been previously considered to bear a direct relationship to the observed cutaneous haemorrhages. Few reports have been found which bear directly on this point and only two (Black and others, 1957; Denko and Schroeder, 1957) dealt directly with bleeding and coagulation studies. Among the battery of blood studies done in the nine patients investigated by Denko and Schroeder (1957), the only test that was consistently abnormal was a positive Rumpel-Leede phenomenon. The decreased capillary resistance reflected by this test was suggested as a contributory factor to the skin haemorrhages observed in patients with hypercortisonism. Increased capillary fragility was demonstrated by a positive Rumpel-Leede phenomenon in six out of seven patients reported by Black and others (1957). In our efforts to measure this

TABLE IV  
SERUM PROTEINS

Patient No.	Fibrinogen (mg.)	Total (g.)	Albumin (g.)	Globulin (g.)	Albumin (per cent.)	Electrophoresis			
						Alpha 1 (per cent.)	Alpha 2 (per cent.)	Beta (per cent.)	Gamma (per cent.)
Normal Values <sup>(10)</sup>					70·8	2·7	5·7	8·3	12·6
1	0·334				57	5	11	7·9	19·1
2	0·342	6·75	3·75	3·0	54·4	5·2	13·1	13·2	14·1
3	0·301	6·70	4·16	2·54	62·2	15·5	11	8·9	12·2
4	0·405	5·7	3·4	2·3					
5	0·411	7·24	4·02	3·22	66·7	3·2	7·9	8·8	13·4
6	0·364	7·20	3·77	3·43	60·2	4·3	10·2	10·4	14·9
7	0·376	7·62	3·7	3·92	52·2	5·2	10·3	11·2	20·8
8	0·292	7·19	3·56	3·63	54·9	8·4	10·0	9·8	16·9
9	0·284				62·7	4·0	9·1	9·5	14·7
10	0·500	7·1	3·0	4·1					
11	0·308	7·17	3·99	3·18	63·5	4·0	9·8	8·5	14·2

capillary function, negative pressure was applied using a fragilimeter and also by the Rumpel-Leede method. By the former technique, nine of ten patients studied had no evidence of a decreased capillary resistance; by the latter, six patients were tested and none showed decreased capillary resistance.

It is difficult to reconcile the wide use of prednisolone for the control of ecchymosis and spontaneous skin petechiae in a variety of haemorrhagic diseases with the occurrence of haemorrhagic lesions in this and other similar reports. At present there appears to be no answer to this apparent paradox.

The ease with which these haemorrhages occur after minor trauma has been demonstrated in several of our patients by slapping the uninvolved forearm of a patient with this tendency with a wooden spatula and observing the rapid development of subcutaneous bleeding. Among the factors which might contribute to this phenomenon is the lack of the normal haemostatic mechanism in the pericapillary tissues. This is supported by the failure to demonstrate any defects in the intravascular coagulation mechanisms and, in our hands, no abnormality in the capillary wall itself. Blunt trauma may cause a rent in the capillary wall which is not immediately plugged, and because of intracapillary pressure more and more cells are extruded through this opening to produce a macroscopic lesion.

In the course of these investigations our attention has again been called to the similarity of the lesions described in this paper to those seen frequently in older people with atrophic senile skin. In these old people the distribution of lesions is the same as that seen in patients with rheumatoid arthritis treated with prednisone, the chief sites being the exposed parts of the body, especially the hands and other areas subject to frequent minor trauma. There are several features common to these two conditions. Both the senile skin and that of the patient with rheumatoid arthritis is atrophic and the lack of the pericapillary fat tissue may deprive both subjects of the protective buffering or cushioning quality of subcutaneous fatty tissue. Another common finding might be a generalized "protein depletion" with alterations in the subcutaneous structures which in some as yet unknown way contributes to the inability to control the capillary injury.

### Summary

Purpuric lesions were observed in 44 of 109 patients (40 per cent.) with rheumatoid arthritis who had received long-term steroid therapy. The

incidence of these skin haemorrhages appeared to be greater since the introduction of the so-called delta-1 or meta drugs. The most common sites of these lesions were the forearms, wrists, and dorsa of the hands and fingers, and they occurred without apparent cause or after minor trauma. Extensive laboratory studies, including coagulation factors, capillary resistance and fragility, and serum electrophoretic patterns, failed to demonstrate the mechanism of production of the observed haemorrhagic lesions.

The ease with which subcutaneous bleeding was produced in a susceptible individual by blunt trauma suggests that the lack of the normal haemostatic mechanism in the pericapillary tissues may be a major contributory factor in this phenomenon. The final explanation for this bleeding tendency must await further study.

The authors acknowledge the valuable assistance of Dr. Kurt von Kaulla in this study.

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### Hémorragies sous-cutanées chez des malades rhumatisants traités par la prednisone

#### RÉSUMÉ

Des lésions de purpura furent observées chez 44 sur 109 malades (40%) atteints d'arthrite rhumatismale et ayant subi une thérapie stéroïde pendant des périodes prolongées. La fréquence de ces hémorragies sous-cutanées semblait avoir augmenté depuis l'introduction des produits nommés delta-1 ou méta. Le plus souvent on trouvait ces lésions aux avant-bras, les poignets, le dos des mains et des doigts; elles survenaient sans cause apparente ou bien après un traumatisme peu important. Des examens de laboratoire minutieux, comprenant les facteurs d'agglutination, la résistance et la fragilité capillaire, et d'étude électrophorétique du sérum, ne révélèrent pas le mécanisme par lequel ces lésions hémorragiques auraient pu se produire.

La facilité avec laquelle une hémorragie sous-cutanée chez un sujet susceptible se produisait après un cognement, suggère que l'absence du mécanisme hémostatique normal dans les tissus péri-capillaires serait un facteur contributif majeur. L'explication finale de cette tendance hémorragique demande des études ultérieures.



**Hemorragias subcutáneas en enfermos reumáticos  
tratados con la prednisona****SUMARIO**

Lesiones de púrpura fueron observadas en 44 de los 109 enfermos (40%) con artritis reumatoide que habían recibido una terapia esteroide durante un período prolongado. La frecuencia des estas hemorragias subcutáneas pareció haber aumentado con la introducción de los productos llamados delta-1 o meta. Se encontraban estas lesiones generalmente en los antebrazos, las muñecas, el dorso de las manos y de los dedos;

aparecían sin causa aparente o después de un leve traumatismo. Investigaciones detalladas de laboratorio, comprendiendo los factores de aglutinación, la resistencia y la fragilidad capilar y el cuadro electroforético del suero, no revelaron el mecanismo por el cual estas lesiones hemorrágicas se producían.

La facilidad con que una hemorragia subcutánea se produce en un sujeto susceptible, sugiere que la ausencia del mecanismo hemostático normal en los tejidos pericapilares sería un factor contribuyente mayor. La explicación final de esta tendencia hemorrágica necesita estudios ulteriores.

## EVALUATION OF HAEMAGGLUTINATION TESTS IN THE DIAGNOSIS OF RHEUMATOID ARTHRITIS

### I. THE S.S.C., F.II S.C., AND F.II L.P. SYSTEMS\*

BY

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#### Objective

Since the reports of Meyer (1922) and Waaler (1940) demonstrating that sera from patients with rheumatoid arthritis potentiated the agglutination of sensitized sheep erythrocytes, many investigators have modified the observed phenomenon in order to devise through it a test which might be diagnostic of this disease. Many modifications have been used in order to make the test more specific and less complicated. The Fourth Division Arthritis Laboratory of New York University-Bellevue Medical Centre, as part of its programme to carry out diagnostic laboratory tests on the various rheumatic diseases (Hartung and Mahood, 1955), has sought to standardize and compare these tests to make them more practical for routine use, and we have also attempted to evaluate their diagnostic accuracy.

#### Tests Used

Three haemagglutination tests for rheumatoid arthritis were performed:

- (1) The Heller I modification of the Rose test, formerly designated as the SEA or SCA test (Heller, Jacobson, and Kolodny, 1949) and now as the S.S.C.† test;
- (2) The Fraction II or gamma globulin modification of Heller, Jacobson, Kolodny, and Kammerer (1954), now referred to as the F. II S.C.† test;
- (3) The Latex Fixation or F.II L.P.† test (Singer and Plotz, 1956).

More sensitive methods utilizing the agglutinating and inhibiting factors of the euglobulin fraction of rheumatoid serum isolated by various techniques (Svartz and Schlossmann, 1953; Ziff, Brown, Badin, and McEwen, 1954) are not at this time suitable for routine diagnostic tests because of their length and complexity.

(1) The S.S.C. test consists essentially of inactivating complement in the patient's serum, absorbing the naturally occurring sheep erythrocyte agglutinin (Forssman antibody) in the test serum, and finally preparing serial dilutions of the latter to which sheep erythrocytes sensitized by anti-sheep erythrocyte rabbit serum are added. These agglutinate in the presence of the rheumatoid factor. The final reading is made after incubation at 37° C. for 1 hr and refrigeration overnight. Heller reported that this test was positive at titres of 1 : 28 and higher.

(2) In a later study, Heller examined the inhibitory effect of Human Plasma Fraction II (gamma globulin) on the S.S.C. test. He also modified the latter, using Fraction II instead of anti-sheep erythrocyte rabbit serum to sensitize the sheep cells. This technique does not eliminate any of the other steps in the S.S.C. test. In addition the sheep cells must be treated with tannic acid before adding the sensitizing amount of F. II globulin. In each of the steps described, the pH of the media must always be adjusted to 8. In the final test, the serum is set up in dilutions of 1 : 28 to 1 : 56,000. For controls, unsensitized sheep cells are added to the test serum. Each time a test is performed, concurrent tests are done with positive and negative reference sera. The test is observed after refrigeration overnight and is positive if agglutination occurs in the test sera of 1 : 56 or higher and the controls check out properly. This test, although of value in diagnosis, is not of practical use in a diagnostic laboratory when simpler tests are available, and was devised by Heller as a research tool by which he was able to show that the reactants in the S.S.C. and F. II S.C. tests were heterogenetically related.

(3) The latex fixation test of Singer and Plotz used latex particles of uniform size instead of sheep erythrocytes. Thus absorption of Forssman antibody from the test serum and also inactivation of complement in the test serum is unnecessary. The latex suspension is sensitized with a specific amount

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† A meeting sponsored by the Arthritis and Rheumatism Foundation was held in the early part of 1957. The topics were Haemagglutination Tests in Rheumatoid Arthritis and the factors involved. It was attended by various workers in this field and because of the confusion of nomenclature these abbreviations were agreed upon.

of F. II fraction of human plasma. The diluent in all steps and to the latex gamma globulin mixture is a glycine-buffer solution of pH 8.2. The final dilution of the test serum is 1 : 20-1 : 5120 and a diluent control is also set up. The tubes are placed in a water bath at 56° C. for 1½ hrs and then centrifuged at 2,300 r.p.m. for 3 minutes. Agglutination of 1 : 20 or greater is considered a positive test. Although not necessary, refrigeration overnight after being in the water bath may help to give better readings.

In the evaluation of the tests described, the diagnostic value of each was weighed in relation to the simplicity of performance. The simplicity of a test such as the F. II L.P. method would not be an advantage if it were not of equal or better diagnostic value. When concurrent tests were performed, it appeared that "positive values" in some of them would have to be changed from the accepted standards by one or more dilutions as many sera from non-rheumatoid patients gave positive tests in lower titre dilutions. Thus, in the S.S.C. test, 1 : 56 was considered positive instead of 1 : 28, and in the F. II L.P. test, 1 : 160 instead of 1 : 20. Singer and Plotz (1957) also believe this latter correction to be justified.

#### Material

The three techniques described were used concurrently to test the sera of 239 patients. The sera were obtained from the University Hospital and Bellevue Hospital, Fourth Division, and from about half of the 43 arthritis clinics in Greater New York.

As part of the service offered by the New York Chapter of the Arthritis and Rheumatism Foundation, our laboratory, since its formation in 1955, has performed approximately 3,800 haemagglutination tests on patients with an established or tentative diagnosis of one of the rheumatic disorders. In 202 of these patients, in whom all three concurrent tests mentioned above were performed, a presumptive diagnosis by the referring physician accompanied the serum sample. The diagnosis of rheumatoid arthritis was made in 147 cases. Of these 134 were classified, according to criteria set up by the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox, and Jessar, 1956), as follows:

Classical or Definite Rheumatoid Arthritis, 83;  
Probable Rheumatoid Arthritis, 24;  
Possible Rheumatoid Arthritis, 27;

The other thirteen patients had other diagnoses:

Gout and/or Rheumatoid Arthritis, 6;  
Psoriatic Arthritis, 3;  
Rheumatoid Spondylitis, 4.

The remaining 55 cases were divided as follows:

Gout, 4;

Osteo-Arthritis, 15;  
Fibrositis, Synovitis, and Periarthritis, 10;  
Collagen Disease, 2 (one of the latter was diagnosed as Disseminated Lupus);  
Polyserositis, 5 (some if not all of these might have been grouped under Collagen Disease);  
Palindromic Rheumatism, 1;  
Rheumatic Fever and Rheumatic Heart Disease, 4;  
Non-Arthritic, Non-Collagen Disease, 14 (these included Diabetes Mellitus, Asthma, Rhinitis, and one case of Multiple Myeloma).

No normal controls were sought since these tests were to help differentiate rheumatoid arthritis from other cases appearing in an arthritis clinic.

Also included in this report is an analysis of the tests of the sera of 274 patients (Table IV) on whom only concurrent S.S.C. and F. II S.C. procedures were performed during the period before the F. II Latex technique was begun in this laboratory.

#### Results

The results are presented in the accompanying Tables. Table I demonstrates the overall comparison of these three tests in 239 patients with all diagnoses. It shows that in 74 cases all three tests were positive and in 124 all three tests were negative. The overall percentage of agreement was 83 per cent. When the results were further resolved the S.S.C. and F. II L.P. tests agreed in 92.2 per cent. and disagreed in 7.8 per cent., the latter including 4.1 per cent. F. II L.P. positive and S.S.C. negative, and 3.7 per cent. S.S.C. positive and F. II L.P. negative. The F. II S.C. and F. II L.P. tests agreed in 89.2 per cent., the disagreement comprised a higher percentage of F. II S.C. positive with F. II L.P. negative (10.4 per cent.). The S.S.C. and F. II S.C. tests agreed in 84.7 per cent., but disagreed in that here even a higher percentage were

TABLE I  
ANALYSIS OF CONCURRENT S.S.C.(S), F. II S.C.(F),  
F. II L.P.(L) TESTS IN 239 PATIENTS (ALL DIAGNOSES)

Tests	No. of Patients	Percentage of Total
S+ F+ L+	74	31.0
S- F- L-	124	52.0
S+ F- L-	6	2.5
S- F+ L+	9	3.7
S- F+ L-	22	9.3
S+ F- L-	3	1.2
S- F- L+	1	0.4

#### SUMMARY OF THE THREE SYSTEMS

Tests	Percentage Agreed	Percentage Disagreed
S.S.C., F. II S.C. F. II L.P. ..	83.0	17.0
S.S.C. and F. II L.P. ..	92.2	7.8
F. II S.C. and F. II L.P. ..	89.1	10.9
S.S.C. and F. II S.C. ..	84.7	15.3

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F. II S.C. positive, with S.S.C. negative (12.9 per cent.). Correlation of these figures shows a higher agreement between the S.S.C. and F. II L.P. tests.

Table II breaks down the results of the three concurrent tests in the diagnosed cases and Table III summarizes the positive tests by diagnosis.

In 75 cases of classical rheumatoid arthritis, all three tests agreed positive in 62.8 per cent. and agreed negative in 25.4 per cent. Further analysis of these results shows that the S.S.C. test was positive in 66.3 per cent., the F. II L.P. in 68.2 per cent., and the F. II S.C. test in 72.2 per cent.

In probable rheumatoid arthritis, the S.S.C. test was positive in 13.6 per cent., F. II L.P. in 9.1 per cent., and F. II S.C. in 27.2 per cent.

In possible rheumatoid arthritis the S.S.C. test was positive in 20.8 per cent., the F. II L.P. in 29.2 per cent., and the F. II S.C. in 37.4 per cent.

It appears that the F. II S.C. test gives more positive results than the others, but it would be superficial to call it more sensitive. This is brought out by analysing the results in 46 cases of non-collagen disease, where the percentage of positive tests was S.S.C. 8.6 per cent., F. II L.P. 4.3 per cent., and F. II S.C. 15.2 per cent. It was noted that where the F. II S.C. was positive and the other two tests negative, the former was usually positive in the lower titres between 1 : 56 to 1 : 448 and rarely in the strong titres of 1 : 3584 or 1 : 7168.

In a previous study, S.S.C. and F. II S.C. tests

TABLE II  
ANALYSIS OF CONCURRENT S.S.C.(S), F. II S.C.(F), F. II L.P. (L) TESTS IN 202 DIAGNOSED CASES

Diagnosis		No. of Cases	S+F+ L+		S-F- L-		S+F- L-		S-F+ L+		S+F+ L-		S-F+ L-		S-F- L+		S+L+		S-L-		S-L+	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Rheumatoid Arthritis	Classical ..	83	47	56.8	19	22.9	2	2.4	4	4.7	1	1.2	2	2.4	—	—	3	3.6	3	3.6	2	2.4
	Probable ..	24	2	8.3	16	66.7	—	—	—	—	1	4.2	3	12.5	—	—	—	—	2	8.3	—	—
	Possible ..	27	4	14.7	14	52.0	1	3.7	3	11.1	—	—	2	7.4	—	—	—	—	2	7.4	1	3.7
Psoriatic Arthritis .. ..		3			3																	
Rheumatoid Spondylitis ..		4	1		2														1			
Gout and/or Rheumatoid Arthritis .. .. .		6	4		1										1							
Gout .. .. .		4			2		1												1			
Osteo-Arthritis .. ..		15			14					1												
Fibrositis, Synovitis, Periarthritis		10	1		8								1									
Palindromic Rheumatism ..		1			1																	
Collagen Disease .. ..		1			1																	
Disseminated Lupus Erythematosus .. .. .		1			1																	
Polyserositis .. .. .		5			2		1						1						1			
Rheumatic Fever .. ..		4			2								2									
Other Diseases, Diabetes Mellitus, etc. .. .. .		14	1		11								1						1			

TABLE III  
POSITIVE RESULTS IN CONCURRENT S.S.C., F. II S.C., AND F. II L.P. TESTS

Diagnosis		No. of Patients	S.S.C.		F. II S.C.		F. II L.P.	
			No.	per cent.	No.	per cent.	No.	per cent.
Rheumatoid Arthritis	Classical ..	75	50	66.3	54	72.2	51	68.2
	Probable ..	22	3	13.6	6	27.2	2	9.1
	Possible ..	24	5	20.8	9	27.4	7	29.2
Non-Rheumatoid Arthritis Diseases (excluding Collagen Diseases, but not Rheumatic Fever) ..		46	4	8.6	7	15.2	2	4.3



were done with 274 cases. Analysis of these results also showed a much higher percentage of positives with the F. II S.C. than with the S.S.C. technique (Table IV). In 108 cases of classical rheumatoid arthritis these tests agree in 76 per cent., but the S.S.C. was positive and the F. II S.C. negative in 6.5 per cent., and the F. II S.C. positive and the S.S.C. negative in 16.7 per cent.

In 58 cases of probable rheumatoid arthritis, the tests agreed in 77.6 per cent., but the S.S.C. was positive and F. II S.C. negative in 5.2 per cent., and the F. II S.C. positive and S.S.C. negative in 17.2 per cent.

In 94 cases of possible rheumatoid arthritis the tests agreed in 71 per cent., but the S.S.C. was positive and the F. II S.C. negative in 5.6 per cent., and the F. II S.C. positive, and S.S.C. negative in 23.4 per cent.

This question was studied further; eighteen patients of the above group in which the S.S.C. and F. II S.C. tests did not agree were retested 3 to 9 months later with new serum samples and repeated diagnoses were made at the time the blood was taken (Table V, opposite). Where an F. II S.C. titre is positive in the lower range, even up to 1 : 448, it may at times revert to a negative test, but that the higher titres rarely fail to remain so. It is rare to see a positive S.S.C. titre become normal without therapy and here again it is in the low titre of 1 : 56 that may become 1 : 28.

In concluding this section dealing with observations, in all three techniques a one-tube difference in titre may occur when the same serum sample is re-tested.

Discussion

Evaluating these three haemagglutination tests for rheumatoid arthritis shows that, with the exception of the F. II S.C. test, they are about equal in sensitivity.

In classical rheumatoid arthritis, the S.S.C. was positive in 66.3 per cent., the F. II L.P. in 68.2 per cent., and the F. II S.C. in 72.2 per cent.

Also in probable and possible rheumatoid arthritis these tests gave higher positive results than for non-rheumatoid and non-collagen diseases. In the latter group, which in this investigation served as controls, the S.S.C. was positive in 8.6 per cent., the F. II L.P. in 4.3 per cent., and the F. II S.C. in 15.2 per cent. It follows that the lowest titre now accepted as positive in the F. II S.C. test, namely 1 : 56, should be increased to a titre of 1 : 448 or 1 : 896. Informal talks with workers in the field and experience with repeat serums in low-positive titres (Table V), show that such a change will make the test more diagnostic and eliminate false positives.

It can be observed here that more than one rheumatoid factor may be involved in these tests, depending on whether anti-sheep erythrocyte rabbit serum or Human F. II globulin is the sensitizing agent, since a substantial number of patients with classical rheumatoid arthritis will give positive S.S.C. and negative F. II S.C. tests and *vice versa*. Heller was the first to show this by means of absorption studies of rheumatoid arthritis sera with the S.S.C. and F. II S.C. methods. He found that, while in the majority of the sera cross-reactions occurred, in some after completion of the S.S.C. test the

TABLE IV  
ANALYSIS OF CONCURRENT S.S.C. AND F. II S.C. TESTS

Clinical Diagnosis			Total No. of Tests	Agree Negative		Agree Positive		S.S.C. Positive F. II S.C. Negative		F. II S.C. Positive S.S.C. Negative	
				No.	per cent.	No.	per cent.	No.	per cent.	No.	per cent.
Rheumatoid Arthritis	Possible ..	..	94	51	54.0	16	17.0	5	5.6	22	23.4
	Probable ..	..	58	25	43.2	20	34.4	3	5.2	10	17.2
	Classical ..	..	108	31	28.6	52	48.2	7	6.5	18	16.7
Classical Rheumatoid Psoriasis .. .. .	Arthritis and ..	..	3	2	66.7					1	33.3
Rheumatoid Series ..	..	..	263	109	41.7	88	33.4	15	5.6	51	19.3
Osteo-Arthritis ..	..	..	4	3	75.0	1	25.0				
Fibrositis .. .. .	..	..	1	1							
Lupus Erythematosus ..	..	..	3	2	66.7			1	33.3		
Psychogenic Rheumatism ..	..	..	1	1							
Bursitis .. .. .	..	..	2	1						1	
Total .. .. .	..	..	274								

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TABLE V

(a) DIAGNOSIS AND CONCURRENT S.S.C., F. II S.C. TESTS IN EIGHTEEN PATIENTS

(b) REPETITION OF THESE TESTS WITH NEW SERUM SAMPLES AND DIAGNOSES 3 TO 9 MONTHS LATER

Patient and Diagnosis				S.S.C. Titre	F. II S.C. Titre
1	a	Classical Rheumatoid Arthritis	..	112	28
	b	"	"	56	28
2	a	"	"	28	3,584
	b	"	"	112	28
3	a	"	"	112	28
	b	"	"	56	1,792
4	a	"	"	14	112
	b	"	"	14	28
5	a	"	"	28	15,000
	b	"	"	56	15,000
6	a	"	"	112	28
	b	"	"	56	28
7	a	Probable Rheumatoid Arthritis	..	28	224
	b	"	"	56	224
8	a	"	"	14	112
	b	"	"	14	7
9	a	"	"	7	224
	b	"	"	14	224
10	a	"	"	56	28
	b	"	"	56	28
11	a	"	"	7	224
	b	"	"	7	28
12	a	"	"	7	112
	b	Possible Rheumatoid Arthritis	..	7	56
13	a	Possible Rheumatoid Arthritis	..	28	3,584
	b	"	"	224	3,584
14	a	"	"	7	112
	b	"	"	7	7
15	a	"	"	14	448
	b	"	"	14	28
16	a	"	"	14	448
	b	"	"	14	28
17	a	"	"	28	7,168
	b	Classical Rheumatoid Arthritis	..	14	1,792
18	a	Possible Rheumatoid Arthritis	..	56	28
	b	Dermatomyositis	..	28	28

supernatant sera would react by the F. II S.C. technique and *vice versa*. He concluded that the rheumatoid factors were heterogenetically related (Heller, Kolodny, Lepow, Jacobson, Rivera, and Marks, 1955). Also to be taken into account is the presence of an inhibitory factor and its effect on the activity of the rheumatoid factors.

There was a higher correlation of results between the S.S.C. and the F. II L.P. techniques. Plotz and Singer (1956) reported that their F. II L.P. results were 71.3 per cent. positive, and our figure is 68.2 per cent.

In tests done with control sera (non-rheumatoid,

non-collagen diseases) our results were not so close. In our series, the F. II L.P. test gave positive reactions in 4.3 per cent., while Plotz and Singer reported a similar control series as 2.5 per cent. positive. One reason for the difference in our figures, as far as the lower incidence of positive tests in classical rheumatoid arthritis is concerned, is that we used 1:160 as our lowest positive dilution, whereas in their original report they set the minimum positive as 1:20. They have since said that it is very rare for a positive serum to be positive only in concentrations below 1:160. We have found a good many positives in only the 1:20 to 1:80 range in non-rheumatoid controls which were negative by the other tests.

Summary

- (1) Concurrent S.S.C., F. II S.C., and F. II L.P. tests in 239 patients with all diagnoses showed agreement in 83.0 per cent. There was a higher degree of correlation between the S.S.C. and F. II L.P. tests.
- (2) In cases of classical or definite rheumatoid arthritis, all three tests agreed positive in 62.8 per cent. The S.S.C. was positive in 66.3 per cent, the F. II L.P. in 68.2 per cent., and the F. II S.C. in 72.2 per cent.
- (3) In cases of probable and possible rheumatoid arthritis the three tests consistently gave more positive tests than in the controls.
- (4) In the control series (non-rheumatoid and non-collagen disease), the S.S.C. was positive in 8.6 per cent., the F. II L.P. in 4.3 per cent., and the F. II S.C. in 15.2 per cent.
- (5) The higher incidence of F. II S.C. positives in all series is due in part to the use of a titre of 1:56 or higher as the positive standard. This value should be changed and the positive titre standardized at 1:896 and higher.
- (6) Analysis of concurrent S.S.C. and F. II S.C. tests of 263 rheumatoid sera show that more than one rheumatoid factor may be present in rheumatoid sera. Factors inhibiting the activity of the rheumatoid factors are also recognized as important.
- (7) All three tests (with allowances for proper standards of positive titres) are equal in sensitivity for routine diagnostic screening.
- (8) The F. II L.P. test is to be preferred to the others because of its simplicity and rapidity, but the lowest titre recognized as positive should be 1:160.

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### L'évaluation des réactions d'hémagglutination dans le diagnostic de l'arthrite rhumatismale

#### I. Systèmes S.S.C., F. II S.C. et F. II L.P.

##### RÉSUMÉ

Les auteurs décrivent ces trois méthodes: la S.S.C. est une modification de la réaction de Rose; dans la F. II S.C., la Fraction II du plasma humain est employée au lieu du sérum lapin-anti-mouton; dans la méthode F. II L.P., une suspension de particules de latex est substituée aux globules rouges de mouton.

(1) Les réactions S.S.C., F. II S.C., et F. II L.P. chez 239 malades avec tous les diagnostics s'accordaient dans 83% des cas. L'accord était plus prononcé entre la S.S.C. et la F. II L.P.

(2) Dans les cas d'arthrite rhumatismale classique ou définie, la pourcentage des trois réactions simultanément positives était 62,8%. La S.S.C. était positive en 66,3%, la F. II L.P. en 68,2%, et la F. II S.C. en 72,2% des cas.

(3) Dans les cas d'arthrite rhumatismale probable et possible il y avait appréciablement plus de réactions positives, selon les trois méthodes, que chez les témoins.

(4) Chez les témoins (n'atteints pas de maladie rhumatismale ou collagène) la réaction S.S.C. était positive chez 8,6%, la F. II L.P. chez 4,3%, et la F. II S.C. chez 15,2%.

(5) La plus grande fréquence des réactions F. II S.C. positives dans toutes les séries est due au fait qu'on avait accepté un titre minimum de 1 : 56 comme standard de positivité; ce standard devrait être changé à 1 : 896.

(6) L'analyse des réactions S.S.C. et F. II S.C. sur les mêmes 263 sérums rhumatismaux a montré qu'il pourrait y avoir plus qu'un facteur rhumatismal. On

reconnaît aussi l'importance des facteurs inhibiteurs de l'activité rhumatismale.

(7) Pour des besoins ordinaires de diagnostic, les trois réactions (tenant compte de standards de positivité des titres) ont une sensibilité égale.

(8) La réaction F. II L.P. est préférable aux deux autres en raison de sa simplicité et rapidité, pourvu qu'on accepte un titre minimum de 1 : 160 comme positif.

### Valoración de reacciones de hemaglutinación en el diagnóstico de la artritis reumatoide

#### I. Sistemas S.S.C., F. II S.C., y F. II L.P.

##### SUMARIO

Los autores describen los tres métodos: la S.S.C. es una modificación de la reacción de Rose; en la F. II S.C., la Fracción II del plasma humano se emplea en lugar del suero conejo-anti-oveja; en la reacción F. II L.P. una suspensión de partículas de latex se ve sustituida a los eritrocitos de oveja.

(1) Las reacciones S.S.C., F. II S.C., y F. II L.P. en 239 enfermos con todos los diagnósticos se acordaron en un 83% de los casos. El acuerdo fue más pronunciado entre la S.S.C. y la F. II L.P.

(2) En la artritis reumatoide clásica o definida, las tres reacciones fueron simultáneamente positivas en un 62,8% de los casos. La S.S.C. fue positiva en un 66,3%, la F. II L.P. en un 68,2%, y la F. II S.C. en un 72,2% de los casos.

(3) En los casos de artritis reumatoide probable y posible hubo apreciadamente más reacciones positivas, según los tres métodos, que en los testigos.

(4) En los testigos (sin enfermedad reumática o colagena) la reacción S.S.C. fue positiva en un 8,6%, la F. II L.P. en un 4,3%, y la F. II S.C. en un 15,2%.

(5) La mayor frecuencia de las reacciones F. II S.C. positivas en todas las series se debe al hecho de haber aceptado un título mínimo de 1 : 56 como norma de positividad. Esta norma se deberá cambiar a 1 : 896.

(6) El análisis concurrente de las reacciones S.S.C. y F. II S.C. sobre 263 sueros reumáticos mostró la posible existencia de más de un factor reumático en estos sueros. Se reconoce también la importancia de factores inhibidores de la actividad reumática.

(7) Para las necesidades ordinarias de diagnóstico, las tres reacciones (tomando en cuenta las normas de positividad de los títulos) tienen una sensibilidad igual.

(8) La reacción F. II L.P. se prefiere a las demás por ser simple y rápida, provisto que se acepte un título mínimo de 1 : 160 como positivo.

## MARROW IRON EXAMINATION IN THE DIAGNOSIS OF IRON DEFICIENCY IN RHEUMATOID ARTHRITIS\*

BY

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A moderate degree of anaemia is commonly present in patients with rheumatoid arthritis. The anaemia is usually normocytic and hypochromic and the degree of anaemia roughly parallels the activity of the disease (Nilsson, 1948; Jeffrey, 1953a). Among the varied features described in anaemia associated with arthritis are alterations in plasma volume causing anaemia through hydraemia (Robinson, 1943; Dixon, Ramcharan, and Ropes, 1955), an increased rate of red cell destruction (Mollison and Paterson, 1949; Bunim, 1954; Freireich, Ross, Bayles, Emerson, and Finch, 1954; Alexander, Richmond, Roy, and Duthie, 1956), and abnormalities in iron and porphyrin metabolism (Jeffrey, 1953b).

The effect of iron therapy on anaemia in this disease has been studied by several workers. Sinclair and Duthie (1950) reported that haemoglobin levels improved with intravenous iron therapy in cases in which oral iron had proved ineffective. Ross (1950) and Jeffrey (1953a) also reported good results with intravenous iron in this condition but all these workers found numerous cases which failed to respond to this treatment. Jeffrey (1953b), in a search for prognostic factors which might indicate whether the anaemia in any given case was likely to respond to intravenous iron, was unable to derive any material help from assessment of many clinical and laboratory features of the disease. Another group of workers (Kuhns, Gubler, Cartwright, and Wintrobe, 1950) stated that the anaemia and hypoferraemia of rheumatoid arthritis were not appreciably influenced by intravenous iron.

Reports on the value of intravenous iron in the treatment of this anaemia are conflicting and the indications for its use are not clear. In view of the possible dangers of this type of therapy, especially in patients who are not iron-deficient (Dameshek, 1950; Holly, 1951), it is desirable that intravenous iron should not be used except in cases of iron-

deficiency anaemia. The first steps in the diagnosis of iron deficiency anaemia are examination of peripheral blood smears and calculation of "absolute values": the mean cell volume (M.C.V.) and the mean cell haemoglobin concentration (M.C.H.C.). In iron-deficiency anaemia of long standing, the red cells are hypochromic and microcytic and there is decrease in the M.C.V. and M.C.H.C. Certain conditions, *e.g.* thalassaemia and the anaemia of chronic infection in which the red cells may be hypochromic, may be confused with chronic iron deficiency from peripheral blood examination alone. In true iron deficiency, however, more specific diagnostic findings are present: the absence of iron from the bone marrow, the absence of iron granules in the normoblasts, and a low serum iron level (Coleman, Stevens, and Finch, 1955). Coleman and his colleagues state that, in their experience, the most reliable and sensitive diagnostic test for iron-deficiency is the absence of iron from the marrow.

Bone marrow examination for iron as a means of assessing body iron stores has been recommended by many workers (Rath and Finch, 1948; Hutchison, 1953; Stevens, Coleman, and Finch, 1953). Although it is not certain that marrow iron is a fair reflection of total iron storage, reports from workers who have investigated iron storage in the liver or spleen concurrently with marrow examination indicate that iron storage in each case was comparable for the various sites at the time (Pratt and Johnson, 1954; Beutler, Drennan, and Block, 1954). It is generally agreed that iron deficiency alone of the conditions studied is characterized by absence of marrow iron (Hutchison, 1953; Stevens and others, 1953). Hutchison (1953) states that the hypochromic anaemia due to iron deficiency can be differentiated from that due to chronic infection or intoxication, by examination of marrow iron. In the former condition there is absence of marrow iron whereas in the latter a varying amount of iron can be demonstrated.

In the work here reported, marrow iron examinations were used to study iron deficiency in cases of rheumatoid arthritis and the effect of intravenous

\* Based on part of a thesis for the degree of M.D. in the Queen's University of Belfast.



iron on the anaemia in these cases was recorded. The cytology of the bone marrow was also studied, particular attention being paid to the maturation of the erythroid series and to the relation between marrow plasma cell levels and serum globulin concentrations.

### Materials and Methods

33 cases, all in-patients, suffering from active rheumatoid arthritis were investigated. Each case was classified as suffering from "slightly active" (+), "moderately active" (++), or "very active" (+++) disease. In classification, the degree of joint pain and tenderness, the presence of general constitutional disturbance, and the erythrocyte sedimentation rate (E.S.R.) were considered. In each case the initial haemoglobin level was 11 g. per 100 ml. or less, the mean corpuscular haemoglobin concentration (M.C.H.C.) was 29 per cent. or less, and the mean cell volume (M.C.V.) was within normal limits or diminished. Two rheumatoid patients had previously suffered blood loss from haemorrhoids, but were not bleeding at the time of this investigation. Two control cases with uncomplicated iron deficiency anaemia due to blood loss were also investigated. One had suffered from repeated epistaxis for some months, and the other was anaemic because of menorrhagia.

Bone marrow examination was carried out in each case before the start of iron therapy. Approximately 1 g. of an iron preparation for intravenous use (saccharated oxide of iron in colloidal solution, either "Iviron" or "Ferrivenin", containing 20 mg. colloidal iron per ml.) was administered in from six to ten injections during a period of 8 to 14 days. As iron was given intravenously, the question of absorption from the gastro-intestinal tract did not arise. Reticulocyte counts were made on at least two occasions between the 5th and 12th days after the start of iron therapy. The results of treatment were assessed at the end of a test period of 4 to 5 weeks. In eight cases observations were continued at the end of the initial trial period, so that, in some cases, the progress of the anaemia was studied for periods of up to 3 months from starting treatment with iron.

**Bone Marrow Examination.**—Marrow puncture was performed in the manubrium or first or second pieces of the body of the sternum under local anaesthesia. Smears were made from the first few drops of marrow aspirated, after which a further quantity (0.5 to 1 ml.) of a mixture of blood and marrow was withdrawn into fixative. Histological sections were prepared from aspirated marrow and were stained for iron by the Prussian blue method, using a modification (Hutchison, 1953) of the technique of Cappell, Hutchison, and Smith (1947). Storage iron is present in the bone marrow in two forms: ferritin and haemosiderin (Pirie, 1950). It is generally believed that only haemosiderin is stained by the Prussian blue method, but Finch, Hegsted, Kinney, Thomas, and four others (1950) stated that large amounts of ferritin in a cell might give a positive reaction. The material giving a positive Prussian blue reaction may not be a

single chemical entity, and the term "stainable iron" is often used in preference to haemosiderin (Hutchison, 1953).

**Examination of Marrow Sections.**—In marrow sections stained by the Prussian blue method, iron is seen in the reticuloendothelial cells giving a diffuse blue colour to the cell or in the form of intracellular granules or as dense clumps. The distribution of iron throughout the marrow is irregular and several fragments are required for examination particularly in order to support a negative finding (Hutchison, 1953).

A rough classification of the marrows with regard to iron content was made:

- (1) Devoid of stainable iron.
- (2) Containing a "small" amount of iron; a few cells showed a diffuse blue coloration and/or more densely staining granules.
- (3) Containing a "moderate" amount of iron; e.g. a larger number of cells showed blue staining of the cytoplasm with numerous granules and perhaps small clumps.
- (4) Containing a "large" amount of iron; densely staining clumps were present.

Where small amounts of iron were present, the result was confirmed by staining a further section. Negative findings were checked by staining a further section in parallel with a section known to be positive for iron.

**Examination of Marrow Smears.**—500 nucleated cells were counted and the myeloid:erythroid ratio was determined. In each case, the percentages of the different types of erythroblasts in a count of 100 nucleated erythroid cells were estimated. Many factors (e.g. the wide variation in the normal range of differential counts, the irregular distribution of marrow cells on smears, and dilution with peripheral blood) make minor alterations in marrow cytology difficult to establish (Dacie, 1950a). Erythroid maturation was studied here by expressing the numbers of different classes of erythroblasts as percentages of the total erythroblast count, rather than as percentages of the total nucleated cells present. In the absence of marked peripheral erythroblastemia, the factor of dilution with peripheral blood does not affect the accuracy of these differential erythroblast counts (Dacie and White, 1949).

**Other Tests.**—Haemoglobin was estimated on samples of venous blood as alkaline haematin in a photoelectric colorimeter, using the artificial standard of Gibson and Harrison (1945). Reticulocytes were counted by the method of Dacie (1950b). Serum protein levels were determined by the Biuret method. Erythrocyte sedimentation rates were measured by Westergren's method.

### Results

A significant response to iron therapy has to be evaluated in the light of physiological fluctuations and errors in haemoglobin measurement (Coleman and others, 1955). Coleman and his colleagues defined a "significant response" as an increase in

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TABLE I  
RESULTS OF MARROW IRON EXAMINATION AND INTRAVENOUS IRON THERAPY

Case No.	Sex	Age (yrs)	Degree of Disease Activity	Initial Haemoglobin Level (g./100 ml.)	M.C.H.C. (per cent.)	Haemoglobin after Iron Therapy (g./100 ml.)	Increase in Haemoglobin (g./100 ml.)	Marrow Iron (amount)	Test Period (days)
1	F	52	+++	10.6	29	11.8	1.2	Large	29
2	M	24	+++	11.0	28	11.7	0.7	Moderate	35
3	M	43	+++	10.7	29	10.2	—	Large	30
4	F	33	+++	10.1	28	9.9	—	Moderate	31
5	F	59	+++	9.9	28	13.8	*3.9	Moderate	35
6	M	56	+++	9.9	28	10.6	0.7	Large	28
7	M	67	++	9.0	25	11.8	*2.8	None	28
8	F	60	+++	10.0	29	9.8	—	Moderate	32
9	M	49	++	8.8	26	12.0	*3.2	None	35
10	F	50	+++	8.0	26	10.7	*2.7	None	31
11	F	68	+++	11.0	29	10.2	—	Large	28
12	M	66	+++	9.0	28	11.7	*2.7	None	32
13	F	55	++	10.7	29	13.1	*2.4	None	26
14	F	39	++	10.6	29	12.0	1.4	None	28
15	F	46	+	10.6	28	13.0	*2.4	None	28
16	F	63	+++	8.8	27	8.3	—	Moderate	35
17	F	49	+	10.7	27	13.6	*2.9	None	28
18	F	61	++	9.1	27	11.2	*2.1	None	28
19	F	60	++	8.5	28	10.6	*2.1	None	28
20	F	70	+++	11.0	29	11.7	0.7	Moderate	30
21	F	29	++	10.1	29	11.4	1.3	Small	28
22	F	65	++	10.7	29	11.4	0.7	Small	29
23	F	44	+++	9.1	28	10.4	1.3	Moderate	30
24	M	57	+++	11.0	28	11.7	0.7	Small	30
25	F	56	++	10.7	29	10.6	—	Moderate	28
26	M	45	+++	9.6	29	10.7	1.1	Large	35
27	M	62	++	6.9	26	10.1	*3.2	None	28
28	F	56	+++	9.6	28	9.1	—	Large	30
29	F	58	+++	10.1	28	10.7	0.6	Moderate	29
30	M	56	+++	8.3	26	9.0	0.7	Large	29
31	F	58	+++	8.2	27	9.0	0.8	Small	35
32	F	55	++	10.7	29	11.7	1.0	Moderate	35
33	F	54	+++	9.9	28	10.7	0.8	Moderate	31

\* Rise in haemoglobin of 2 g./100 ml. or more.

TABLE II  
RESULTS OF INTRAVENOUS IRON THERAPY IN TWO CONTROL CASES

Clinical Diagnosis	Sex	Age (yrs)	Initial Haemoglobin (g./100 ml.)	M.C.H.C. (per cent.)	Haemoglobin after Iron Therapy (g./100 ml.)	Increase in Haemoglobin (g./100 ml.)	Trial Period (days)
Epistaxis .. ..	M	58	6.4	25	12.3	5.9	28
Menorrhagia .. ..	F	44	9.0	26	13.4	4.4	30

haemoglobin of 2 g. per 100 ml. or more. In assessing the results of the present investigation this same arbitrary response level has been used.

The results are given in Table I. In eleven cases no stainable marrow iron was present. In ten of these eleven cases the haemoglobin level rose by more than 2 g. per 100 ml. In one patient (Case 14) the rise in haemoglobin was only 1.4 g. per 100 ml. With one exception (Case 10), the patients in this group suffered from only moderately or slightly active disease. The average rise in haemoglobin in the ten cases was less than that seen in the control cases who suffered from uncomplicated iron deficiency anaemia (Table II). The reticulocyte counts in the arthritic patients were low in comparison with those observed in the control cases (Table III).

TABLE III  
MAXIMUM RETICULOCYTE COUNTS IN PATIENTS WHO RESPONDED TO IRON THERAPY

(Ten Patients with absent marrow iron and two control patients)

Group	Case No.	Sex	Age (yrs)	Initial Haemoglobin (g./100 ml.)	Maximum Reticulocyte Response (per cent.)
Control	Epistaxis	M	58	6.4	11.5
	Menorrhagia	F	44	9.0	5.4
Marrow Iron Absent	7	M	67	9.0	2.2
	9	M	49	8.8	4.2
	10	F	50	8.0	2.3
	12	M	66	9.0	2.5
	13	F	55	10.7	3.9
	15	F	46	10.6	2.5
	17	F	49	10.7	1.7
	18	F	61	9.1	1.3
	19	F	60	8.5	3.5
	27	M	62	6.9	5.5

In 22 cases a varying amount of marrow iron was demonstrated. The haemoglobin level rose by 2 g. per 100 ml. or more in only one patient (Case 5). This patient had improved clinically and there was a marked fall in the erythrocyte sedimentation rate during the trial period.

Ten of eleven cases (91 per cent. in which the marrow was devoid of iron responded to iron by a rise in haemoglobin of more than 2 g. per 100 ml. Only one of the 22 cases (5 per cent. in which iron was demonstrated showed a response. Although computed on a small number of cases, the difference in the two response rates (91 as against 5 per cent.) could not have arisen by chance.

The results of follow-up studies in eight cases which were refractory to iron therapy in the initial trial period are given in Table IV. No appreciable rise in haemoglobin occurred in any case over the longer period of observation.

**Marrow Cytology.**—A summary of the findings is given in Table V. There is no marked hyperplasia of the erythroid series, only seven cases showing myeloid:erythroid ratios of 2:1 or less. Examination of marrow sections confirmed that there were no gross hyperplasia. In most cases, the numbers of basophilic normoblasts were increased when the figures were compared with those given for fifteen

TABLE IV  
RESULTS OF FOLLOW-UP STUDIES IN IRON-REFRACTORY CASES

Case No.	Sex	Age (yrs)	Before Iron Therapy		After Iron Therapy		Time (days)
			Haemoglobin (g./100 ml.)	E.S.R. (mm./hr)	Haemoglobin (g./100 ml.)	E.S.R. (mm./hr)	
2	M	24	11.0	68	12.5	52	96
3	M	43	10.7	98	11.8	90	75
4	F	33	10.1	66	9.9	62	97
8	F	60	9.4	78	9.9	80	41
11	F	68	11.0	66	12.0	48	74
16	F	63	8.8	120	8.5	94	70
20	F	70	11.0	60	11.2	62	97
23	F	44	9.1	62	10.7	43	55

TABLE V  
MARROW CYTOLOGY

Case No.	Myeloid : Erythroid Ratio	Pro-Normoblasts*	Basophilic Normoblasts*	Polychromatic Normoblasts*	Pyknotic Normoblasts*	Plasma Cells (per cent.)
1	4 : 1	1	7	58	34	1.4
2	5.4 : 1	—	4	69	27	1.4
3	5 : 1	1	12	73	14	3.2
4	2.7 : 1	3	7	68	22	1.0
5	2.2 : 1	3	15	66	16	1.0
6	4 : 1	2	17	67	14	2.2
7	5.5 : 1	1	5	55	39	0.6
8	2.2 : 1	1	12	69	18	3.2
9	2.1 : 1	1	5	46	48	0.8
10	6 : 1	3	14	49	34	0.2
11	2.4 : 1	4	19	57	20	3.8
12	2.6 : 1	3	10	61	26	0.8
13	3 : 1	1	15	28	56	1.6
14	3.2 : 1	1	11	74	14	0.2
15	2.5 : 1	4	18	47	31	1.2
16	2.7 : 1	1	14	69	16	2.4
17	2.6 : 1	3	13	61	23	2.0
18	3.8 : 1	2	14	54	30	1.2
19	1.2 : 1	1	6	54	39	2.2
20	1.6 : 1	4	20	54	22	0.6
21	3.5 : 1	1	12	65	22	1.2
22	0.8 : 1	1	12	57	30	0.8
23	2 : 1	2	10	70	18	0.8
24	3.8 : 1	3	11	51	35	1.4
25	6 : 1	4	21	50	25	1.6
26	2.1 : 1	1	14	64	21	4.2
27	2.8 : 1	1	7	53	39	0.2
28	1.8 : 1	3	17	60	20	3.0
29	2.1 : 1	1	17	73	9	1.4
30	1.6 : 1	2	21	48	29	4.0
31	1.8 : 1	5	37	34	19	4.2
32	4 : 1	1	22	58	19	1.8
33	3.5 : 1	2	19	52	27	0.8
Normal Series of Dacie and White (1949)		2	5	51	42	—

\* Percentage per 100 nucleated erythroid cells counted.

normal individuals by Dacie and White (1949). This increase was seen both in marrows which contained iron and in those which were devoid of iron. The basophilic normoblasts appeared to be of normal size, but in most cases some of the more mature normoblasts were smaller than normal. These micronormoblasts were seen in marrows which contained iron and in marrows in which no iron was demonstrated, but they were more plentiful in the marrows of the iron-deficient group, *e.g.* Cases 7, 9, and 27. The myeloid series showed no marked deviation from normal. Plasma cell levels were greater than 2 per cent. in ten of the 33 cases examined. In nine cases in which serum globulins were estimated, the results show that plasma cell levels greater than 2 per cent. were constantly associated with serum globulin concentrations of more than 3 g. per 100 ml., although hyperglobulinaemia was not invariably accompanied by marrow plasmacytosis (Table VI). In all cases megakaryocytes were plentiful, but in some they appeared to be present in relatively larger numbers.

TABLE VI  
MARROW PLASMA CELLS AND SERUM  
GLOBULIN LEVELS

Case No.	Sex	Age (yrs)	Marrow Plasma Cells (per cent.)	Serum Globulin (g./100 ml.)
3	M	43	3.2	4.4
26	M	45	4.2	4.2
27	M	62	0.2	2.7
28	F	56	3.0	3.4
29	F	58	1.4	5.2
30	M	56	4.0	4.0
31	F	58	4.2	3.2
32	F	55	1.8	2.4
33	F	54	0.8	3.2

### Discussion

In eleven of 33 patients examined, no marrow iron was demonstrated. Losses due to menstruation, pregnancy, and lactation were possible sources of iron depletion in the seven females in this group. Two of the four male patients had a history of bleeding from haemorrhoids. No explanation for the reduced iron stores in the remaining two male patients was found. Only one patient in this group failed to respond to iron therapy.

In the remaining 22 cases a varying amount of marrow iron was demonstrated. The single case in which there was a considerable rise in haemoglobin, had undergone marked clinical improvement during the period of investigation. Previous workers (Sinclair and Duthie, 1949, 1950; Ross, 1950; Jeffrey, 1953b) have reported that intravenous iron frequently improves the anaemia associated

with arthritis, but Kuhns and others (1950) found that the anaemia was not appreciably influenced by large doses of iron given intravenously. Sinclair and Duthie (1950) noticed a striking fall in the erythrocyte sedimentation rate in many of their cases which responded, a finding which suggests that clinical improvement in the disease could not be excluded as the cause of the rise in haemoglobin. Ross (1950) suggested that a "lag" period existed before intravenous iron produced its maximum effect. The results of iron therapy, Ross claimed, were better after a trial period of 3 months than after one month. The results of follow-up studies in the present series do not bear out Ross's observation, no appreciable haematological improvement taking place so long as disease activity persisted (Table IV). Though the assessment of haematological improvement by peripheral blood figures alone, without reference to the total circulating haemoglobin as determined by the blood volume, may be fallacious (Whitby and Britton, 1953), the response of an anaemia to any given therapy is usually judged by the degree of reticulocytosis and by the rise in haemoglobin. Since the degree of reticulocytosis is variable, depending, for example, on the severity of the anaemia, it is usually more appropriate to determine the effectiveness of iron therapy from the rise in haemoglobin (Coleman and others, 1955). In the present study, the responses to iron therapy in the iron-deficient rheumatoid group are only moderate when compared with those observed in the control cases who suffered from uncomplicated iron deficiency. With one exception, the iron-deficient rheumatoid group suffered from only moderately or slightly active disease, and, in general, the degree of anaemia present in this group was out of proportion to the severity of the disease. The higher haemoglobin levels which were found after response to iron therapy were more in keeping with those to be expected if the anaemia had been due to disease activity alone. Stevens (1956) points out that absence of marrow iron, though an indication that iron stores are reduced, does not guarantee that iron deficiency is the only cause of the anaemia. This is the possible explanation, for the poor response to iron therapy of Case 14 in which the marrow was devoid of iron. It might also explain the incomplete response to iron noticed by Jeffrey (1953b) in cases of anaemia associated with rheumatoid arthritis. In these cases, although the blood picture improved after iron therapy, the haemoglobin failed to return to normal. In one case in the present study (Case 18), after an initial response to iron therapy, the anaemia became refractory to further intravenous iron therapy at



the higher haemoglobin level reached. It is possible that anaemia in certain cases of rheumatoid arthritis is only partially due to iron deficiency. When this iron deficiency is corrected, the residual anaemia in these cases, like the anaemia in the iron-refractory group, may be due to a toxic factor or factors associated with disease activity.

Previous reports on marrow iron stores in cases of rheumatoid arthritis indicate that some marrow iron was present in the majority. Pratt and Johnson (1954) found iron storage greater than normal in four of five anaemic rheumatoid patients. Richmond, Gardner, Roy, and Duthie (1956) examined sternal marrow samples from 61 patients with rheumatoid arthritis and anaemia. In nineteen cases no stainable iron was demonstrable. Iron was present in varying amount in the remaining 42 cases. There is evidence that all marrow iron is available for haemoglobin production. Hutchison (1953) pointed out that the absence of marrow iron in iron-deficient states was proof that all forms of stainable marrow iron could be used for haemoglobin synthesis. Finch and others (1950) concluded, from the results of phlebotomy experiments in dogs, that all intracellular iron was available for haemoglobin production should the need arise. The marrow iron stores in anaemic rheumatoid patients presumably represent iron which, though available, has not been used for haemoglobin reproduction. This does not mean, however, that the primary defect in erythropoiesis is an inability of the developing cells to utilize iron. For example, in a case of pernicious anaemia associated with rheumatoid arthritis investigated by the author, a large amount of marrow iron was demonstrated, and after vitamin B<sub>12</sub> therapy the blood picture improved. In this instance the utilization of iron was impaired because of deficiency of vitamin B<sub>12</sub>. Spontaneous improvement in the anaemia associated with rheumatoid arthritis has been described (Jeffrey, 1953a). Although the importance of alteration in plasma volume in producing a rise in haemoglobin in association with clinical remission in this disease has been stressed (Dixon and others, 1955), it seems reasonable to assume that, when spontaneous improvement does take place, marrow iron stores are utilized for haemoglobin synthesis. In patients whose iron stores are small, the possibility exists that, should clinical improvement occur, the amount of storage iron might be insufficient to restore the haemoglobin to normal. If this were the case, these patients would then require iron therapy to correct the anaemia.

In the majority of the bone marrows examined,

the percentage of basophilic normoblasts was increased (Table V). A similar change in the erythroid series in cases of rheumatoid arthritis was noted by Nilsson (1948). This disturbance of maturation was present both in marrows which were devoid of iron and in those which contained iron. The work of Thorell (1947) and of Hammarsten, Thorell, Åqvist, Eliasson, and Åkerman (1953) suggests that haemoglobin synthesis starts after the basophilic normoblast stage. The experiments of Lajtha and Suit (1955), who measured the uptake of radio-iron by nucleated red cells *in vitro*, indicate that iron uptake is maximal in the late pronormoblast and basophilic normoblast stage. It is possible that the presence of a large percentage of basophilic normoblasts may be indicative of a state in which haemoglobin synthesis is retarded, either because iron is lacking as in iron deficiency, or because of non-utilization of iron as in states characterized by bone marrow dysfunction. This view receives support from the observations of Leitner, Britton, and Neumark (1949) that the percentage of basophilic normoblasts is increased in the bone marrow of patients with iron deficiency anaemia. Marrow plasma cell levels were slightly increased in ten of the 33 cases examined in the present study (Table V). Marrow plasmacytosis in rheumatoid arthritis has been noted by several authors (Hayhoe and Smith, 1951; Klein and Block, 1953; Richmond and others, 1956). In the series of cases examined by Richmond and others (1956), the marrow plasma cell counts were significantly related to the serum globulin level, though hyperglobulinaemia was not invariably associated with marrow plasmacytosis. The findings in the present study confirm their observations, in that hyperglobulinaemia was not constantly accompanied by marrow plasmacytosis although a raised serum globulin level was always found in cases in which an increase in marrow plasma cells was a feature (Table VI). Plasmacytosis appears to be a non-specific response, as it is found in neoplastic, granulomatous, infectious, and allergic states (Klein and Block, 1953).

The exact cause of the anaemia in rheumatoid arthritis is not known. A significant increase in plasma volume in anaemic patients with arthritis has been described (Robinson, 1943; Dixon and others, 1955) and an increased rate of red cell destruction has been demonstrated in this disease (Bunim, 1954; Freireich and others, 1954; Alexander and others, 1956). In a study of the life-span of normal red cells in the circulation of patients with rheumatoid arthritis (McCrea, 1957), six of the iron refractory group of patients were examined; five of these six patients, Cases 28-32, eliminated normal

red cells at two to four times the normal rate. It is unlikely, however, that an increase in plasma volume and an increased rate of red cell destruction could completely account for anaemia in rheumatoid arthritis, particularly in view of the abnormalities in iron metabolism that have been described in this disease (Nilsson, 1948; Jeffrey, 1953b). In some cases in the present study, iron deficiency played a part in the production of anaemia. The factors responsible for anaemia in the patients who failed to respond to intravenous iron therapy and for the residual anaemia after incomplete response to iron are not completely understood. Though an increased rate of red cell destruction is of importance in causing anaemia in some of these cases, a further fundamental defect is the inability to produce fully haemoglobinized red cells despite the presence of unutilized iron stores. The exact nature of this defect is unknown, but in the present study it was not corrected by intravenous iron therapy.

In this work, a response to iron therapy could not have been predicted from peripheral blood examination alone, as the majority of the patients failed to respond despite the fact that the M.C.H.C. was lowered in each case. A much more reliable indication of the probable success or failure of intravenous iron therapy was afforded by marrow iron examination. Iron was given intravenously rather than orally in the present study so that the question of failure of absorption from the intestinal tract might not arise. It has been shown that absorption of oral iron in anaemic patients with rheumatoid arthritis is normal (Roy, Alexander, and Duthie, 1955). If this be so, oral iron should be as effective as parenteral iron in the treatment of iron deficiency anaemia associated with rheumatoid arthritis.

### Summary

Iron deficiency in rheumatoid arthritis was studied by means of marrow iron examinations using the Prussian blue method. The presence of iron in the bone marrow showed that the majority of cases were not iron deficient although the mean cell haemoglobin concentration (M.C.H.C.) was lowered in each case. The reliability of marrow iron examination as a means of detecting iron deficiency in this disease was confirmed by the results of intravenous iron therapy.

In eleven cases, the bone marrow was devoid of stainable iron. With one exception, the anaemia in these patients responded to intravenous iron by a rise in haemoglobin of more than 2 g. per 100 ml. In 22 cases, a varying amount of marrow iron was demonstrated. The haemoglobin level rose by more than 2 g. per 100 ml. in only one case in this group,

and in this patient clinical improvement could not be excluded as the cause of the rise in haemoglobin.

The rise in haemoglobin in iron deficient rheumatoid patients was in general, less than that seen in patients suffering from uncomplicated iron deficiency anaemia. It is suggested that anaemia in some cases of rheumatoid arthritis may be only partially due to iron deficiency. When this iron deficiency is corrected, the residual anaemia, like that in the iron-refractory group, may be due to a toxic factor or factors associated with disease activity.

In many cases there was evidence of a delay in erythroid maturation, in that the number of basophilic normoblasts, expressed as a percentage of total marrow erythroblasts, was increased. This was a feature both of marrows which contained iron and of those which were devoid of iron.

There was a slight increase in marrow plasma cells in ten of the 33 patients examined. In cases in which serum globulin levels were measured, it was observed that marrow plasmacytosis was always associated with a raised serum globulin level, although hyperglobulinaemia was not invariably accompanied by marrow plasmacytosis.

I am indebted to Dr. J. V. Wilson for his help in many ways; to Drs. I. M. P. Dawson and J. J. R. Duthie for criticism and discussion; to Mr. H. Gibson, A.I.M.L.T., for the histological preparations; to the physicians of the Royal Bath Hospital, Harrogate, for allowing me to investigate patients under their charge, and to many members of the nursing and laboratory staffs of the Harrogate Hospitals for co-operation.

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#### Examen du fer de la moelle pour le diagnostic de la déficience en fer dans l'arthrite rhumatismale

##### RÉSUMÉ

On a étudié la déficience en fer dans l'arthrite rhumatismale par l'examen du fer de la moelle osseuse à l'aide du bleu de Prusse. La présence de fer dans la moelle a montré que dans la majorité des cas il n'existait pas de déficience en fer, bien que la concentration moyenne d'hémoglobine globulaire fût toujours abaissée. Les résultats de l'administration intraveineuse de fer ont confirmé la sûreté de l'examen du fer médullaire comme moyen de mettre en évidence la déficience en fer dans l'arthrite rhumatismale.

Dans onze cas, la moelle osseuse était dépourvue de fer colorable. A une exception près, l'anémie chez ces malades a réagi à l'administration de fer par voie intraveineuse par une augmentation de l'hémoglobine au dessus de 2 grammes par 100 cc. Dans 22 cas on a mis en évidence la présence d'une quantité variable de fer dans la moelle. Le taux d'hémoglobine s'est élevé au dessus de 2 g. par 100 cc. dans un seul de ces cas et cette augmentation aurait pu être due à l'amélioration clinique.

L'augmentation d'hémoglobine chez les rhumatisants déficients en fer était en général moindre que celle observée chez des malades souffrants d'anémie hypochrome simple. Il est suggéré que dans certains cas d'arthrite rhumatismale l'anémie puisse n'être que partiellement due à une déficience en fer. Quand cette déficience en fer est corrigée, l'anémie résiduelle, comme celle du groupe réfractaire au fer, peut être due à un ou plusieurs facteurs toxiques associés à l'activité morbide.

Dans plusieurs cas il y avait des signes d'un délai dans la maturation érythroïde, en ce sens que le nombre de normoblastes basophiles, exprimé en pourcentage du total d'érythroblastes médullaires, était augmenté. Ceci constituait un trait à la fois des moelles qui contenaient du fer et de celles qui en étaient dépourvues.

On a trouvé une légère augmentation des plasmocytes médullaires chez 10 des 33 malades examinés. Quand on déterminait le taux de globuline sérique, on observait que la plasmocytose médullaire était toujours associée à une augmentation du taux de globuline sérique, bien que l'hyperglobulinémie ne fût pas invariablement accompagnée par de la plasmocytose médullaire.

#### Examen del hierro medular en el diagnóstico de la carencia férrica en la artritis reumatoide

##### SUMARIO

Se estudió la deficiencia férrica en la artritis reumatoide por el examen del hierro en la médula ósea por el método de azul de Prusia. La presencia de hierro en la médula ósea mostró que en la mayoría de los casos no hubo deficiencia férrica, aunque la concentración media de hemoglobina globular fuese siempre disminuida. Los resultados de administración endovenosa de hierro confirmaron la exactitud del examen del hierro medular como medio de evidenciar la deficiencia férrica en la artritis reumatoide.

En once casos hierro colorable no fué encontrado en la médula ósea. Con una excepción, la anemia en estos enfermos respondió a la medicación férrica endovenosa por un ascenso de la hemoglobina a más de dos gramos por 100 cc. En 22 casos se evidenciaron cantidades variables de hierro en la médula. En un solo de estos casos la cifra de hemoglobina rebasó el 2 gramos por 100 cc. y hasta en este caso el aumento podría atribuirse a una mejoría clínica.

El aumento de hemoglobina en los reumáticos con deficiencia férrica fué generalmente menor que el observado en enfermos con anemia ferripriva simple. Se sugiere que en ciertos casos de artritis reumatoide la anemia se debería tan solo en parte a una deficiencia férrica. Al corregir esta deficiencia, la anemia residual, como en el grupo refractario al hierro podría deberse a uno o más factores tóxicos asociados a la actividad mórbida.

En varios casos se vieron signos de demora en la maduración eritroide, en el sentido de que la cifra de normoblastos basófilos expresada en el porcentaje del total de eritroblastos medulares, fué aumentada. Esto constituyó un rasgo característico tanto de las médulas que contuvieron hierro como de las que fueron desprovistas de él.

En 10 de los 33 enfermos investigados encontrase una ligera aumentación en la cifra de los plasmocitos medulares. Al determinar las cifras de globulina sérica se observó que la plasmocitosis medular fué siempre asociada a un aumento de éstas, aunque una hiperglobulinemia no se vió necesariamente acompañada de plasmocitosis medular.



OSTEO-ARTHRITIS OF THE STERNO-CLAVICULAR JOINT\*

BY

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According to Langen (1934), who made an extensive study of the pathology of degenerative processes in the sterno-clavicular joint in 200 necropsies, it may be involved from the age of 20 and constantly shows signs of osteo-arthritis after the age of 50.

However, few authors seem to have made clinical observations of degenerative disease at this site (Bonola and Mastragostino, 1954; Westermann, 1942).

Having noticed the precocity and functional severity of involvement of this joint in two cases in which surgery was performed, we became interested in the clinical and pathological picture of the disease and also made a study of material brought to necropsy.

Material

The first group of patients was discovered among fifteen who complained precisely and exclusively of pain in the sterno-clavicular joint; eight of them proved to have sterno-clavicular osteo-arthritis (Table I).

TABLE I  
PATIENTS PRESENTING WITH A PAINFUL STERNO-CLAVICULAR JOINT

Diagnosis	Number of Cases		
	Proved	Probable	Total
Tuberculosis .. ..	1	1	2
Staphylococcal Infection ..	1	1	2
Rheumatoid Arthritis ..		1	1
Osteo-Arthritis .. ..	2	6	8
Undetermined .. ..			2

A further group of four patients was found among 200 successive cases of rheumatism seen in the out-patient department. A careful clinical examination of the sterno-clavicular joints showed that 82 patients showed one or more of the following abnormalities: asymmetry, creaking, hypertrophy, tenderness, painful limitation of movement. The

\* This work was done in the Laboratoire d'Anatomie-pathologique de Chirurgie Sud, Hôpital de Purpan, with grants from L'Institut National d'Hygiène (Professor L. Bugnard), and La Caisse Nationale de Sécurité Sociale.

200 cases were classified in four groups (peripheral rheumatoid arthritis, rheumatoid spondylitis, generalized osteo-arthritis, other rheumatic conditions), and among the 25 cases of generalized osteo-arthritis were 21 with abnormal sterno-clavicular joints. Four of these patients volunteered the information that the joint was painful (Table II).

TABLE II  
ABNORMAL STERNO-CLAVICULAR JOINTS IN 200 "RHEUMATIC" PATIENTS

Diagnosis	No. of Patients	Sterno-Clavicular Joints	
		Clinically Abnormal	Painful
Peripheral Rheumatoid Arthritis	29	10	0
Rheumatoid Spondylitis ..	12	0	0
Generalized Osteo-Arthritis ..	25	21	4
Backache, Fibrositis, Psychogenic Rheumatism, etc ..	134	51	0

This study is based on these twelve spontaneously painful cases of sterno-clavicular osteo-arthritis, in all of whom radiological evidence of the degenerative process was found.

It is difficult to estimate the true frequency of this form of osteo-arthritis; it is not usually painful, but most of the physical abnormalities found by clinical examination (such as asymmetrical hypertrophy with or without tenderness) appeared to be due to osteo-arthritis at this site. The frequency of these abnormalities increased with age (Table III), as did the frequency of degenerative lesions in the necroptic series reported by Langen (1934).

TABLE III  
PERCENTAGE FREQUENCY WITH AGE OF AFFECTED JOINTS

Age Group (yrs)	18-29	30-39	40-49	50-59	60-69	70+
200 Necropsies (Langen, 1934)	3	17	48	63	81	100
200 "Rheumatic" Patients (Present series)	17	31	28	50	63	75



**Clinical Data.**—Our twelve patients were all women, ten between the ages of 49 and 66, and the other two aged 30 and 33 respectively. Six had Heberden's nodes and the others had osteo-arthritis at various sites, four of them in the spine or the knee. In all cases the osteo-arthritis of the sterno-clavicular joint was unilateral, on the right side in seven and on the left in five.

The pain was usually moderate, localized to the joint, and of short duration (days or weeks). The two younger patients, however, had very severe and long-lasting pain (1½ and 4 years respectively). The pain radiated in three directions, to the lateral aspect of the neck, to the shoulder joint, and to the breast, and was increased by active motion of the shoulder, particularly abduction, and by pressure upon the joint.

Among the physical signs, firm hypertrophy of the proximal end of the clavicle was constantly and easily found. In six cases passive mobilization of the shoulder produced aching and creaking in the sterno-clavicular joint. The movement of the joint itself seemed to be slightly limited, but in one case the joint was very loose.

**Radiological Data.**—In order to obtain a satisfactory and comparative antero-posterior view of both sterno-clavicular joints, standard techniques are usually insufficient, and we therefore used the technique described by Zimmer (1939) and/or tomography.

General enlargement of the proximal end of the clavicle was observed in each of our twelve cases. Condensation of the clavicular end was seen in ten cases; it was limited, thin and subchondral, or diffuse and spotted. In seven cases an osteophyte was growing outwards from the inferior margin of the end of the clavicle. We also looked for signs of narrowing of the joint space, but this was very difficult to see.

**Clinical Course.**—The course of sterno-clavicular osteo-arthritis may be comparable to that of Heberden's nodes. It may be painful for a few days or weeks during the early stages of development, and may be complicated sooner or later by transitory aching and swelling. We saw many cases which were completely asymptomatic, but in a few undoubted cases the pain was severe and long-lasting in spite of medical and physical treatment.

#### Pathological Data

The basic lesions have been described by Langen (1934). The lesions are cartilaginous with fibrillation and fraying, followed by fissures progressing

from the joint surface to the bone. Nests of newly-formed chondrocytes appear near the border of these fissures. This stage is followed by a proliferation of the subchondral connective tissue of the marrow spaces, which crosses the subchondral plate into the deeper part of the cartilage, which is invaded, destroyed, and replaced by this fibro-vascular tissue. Finally, this new tissue becomes ossified to form new bone and osteophytes. This picture closely resembles that of osteo-arthritis in any joint.

Sokoloff and Gleason (1954) have confirmed this description, and have also suggested the possibility of cystic necrosis of the subchondral bone.

In our own material, comprising two operated cases and 22 joints obtained by necropsy, cartilage fraying, irregular chondrocytic proliferation, and rupture of the calcified line by medullary connective tissue were perfectly seen (Figs 1, 2, and 3). In one of the operated cases (Fig. 3) there was cystic formation in the subchondral bone, and an increase in the number and thickness of the bone trabeculae of the end of the clavicle, which accounted for the remarkable condensation seen in the x-ray plate.



Fig. 1.—Case 1, a woman aged 33, proximal end of left clavicle, showing cartilage fibrillation and irregular proliferation of chondrocytes. Haematoxylin and eosin  $\times 60$ .

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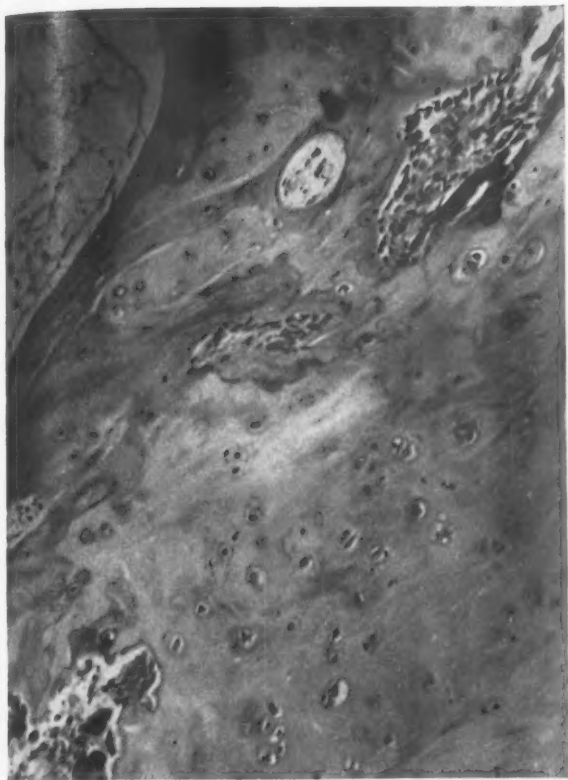


Fig. 2.—Case 1, showing disruption of cartilage by fibrovascular tissue from marrow space. Haematoxylin and eosin  $\times 115$ .

Among the 22 necropsy specimens of joints, which were x-rayed before decalcification, were two with severe osteo-arthritis which presented the same bony condensation.

In two joints, clefts or pseudo-cystic cavities were seen in the centre of the articular cartilage.

#### Treatment

In all cases but two, simple measures (aspirin, phenylbutazone, and/or local injection of hydrocortisone acetate) were sufficient to cause the pain to disappear completely.

In the two cases in young women, in spite of medical treatment and x-ray therapy in one and the use of a plaster cast in the other, very severe pain persisted and it was finally decided to perform a resection of the proximal end of the clavicle end (Figs 4 and 5, overleaf). This was an easy procedure and the functional result was very good. Each case was followed for 18 months after the operation.

Surgery is very rarely indicated in sterno-clavicular osteo-arthritis, but it is well to know that it may be resorted to in severe cases.

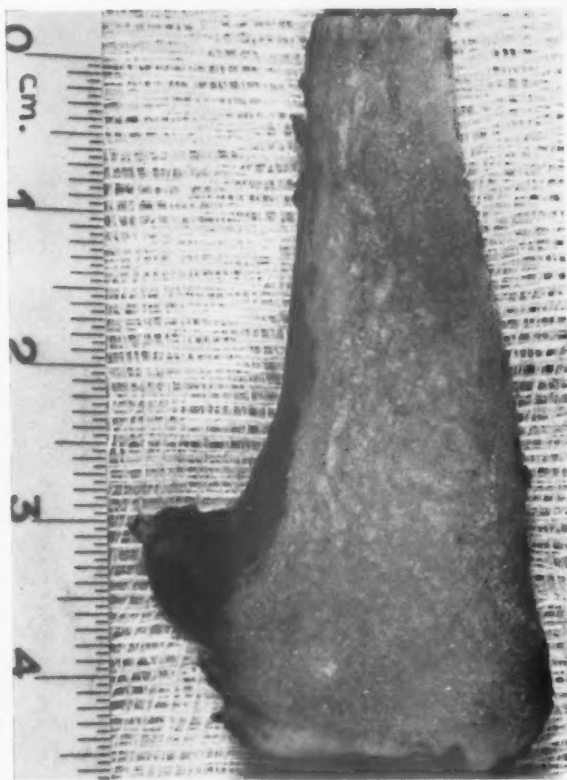


Fig. 3.—Case 2, a woman aged 30, proximal end of left clavicle, showing cartilage erosion and destruction, disruption of cartilage by connective tissue from marrow spaces, and cystic necrosis of subchondral bone. Haematoxylin and eosin  $\times 25$ .

#### Pathogenesis

The aetiology of osteo-arthritis includes mechanical, genetic, and dystrophic factors.

The first must play an important part, since the sterno-clavicular joint is subjected to constant pressure in the orthostatic position.

It is generally agreed that a genetic factor is present in Heberden's nodes and in generalized osteo-arthritis (Stecher, 1955). In our experience the sterno-clavicular joint is clinically abnormal in most cases of generalized osteo-arthritis (in 21 cases out of 25 in our series), and this joint is usually one of the affected sites.

Dystrophy during growth favours the development of spinal osteo-arthritis, and may also affect the development of sterno-clavicular osteo-arthritis. The nucleus of ossification of the proximal end of the clavicle is the last to appear, and growth may continue until the 28th year. This growth may be interrupted, particularly by heavy work, and this may cause non-development or maldevelopment of the clavicular end, as in the case of Friedrich (1924) and in one of our necropsy cases. In fifteen of our



Fig. 4.—Case 1, anterior part of resected proximal end of left clavicle, showing precocious osteo-arthritis of left sterno-clavicular joint.

61 "rheumatic" patients under 40 years of age, the sterno-clavicular joint was clinically abnormal, and in four of them the joint was painful on pressure and movement. In three of these patients the growth of the spine had been disturbed, and in the fourth the tarsal scaphoid was maldeveloped.

#### Summary

Osteo-arthritis of the sterno-clavicular joint was found in twelve patients who complained of pain in this region. In two cases the pain was so severe and intractable that surgical resection was performed with a good result. These were early cases of osteo-arthritis in women aged 30 and 33 years respectively. The diagnosis was proved by histological examination.

The pathological data in these twelve patients were reinforced by the study of 22 cases coming to necropsy.

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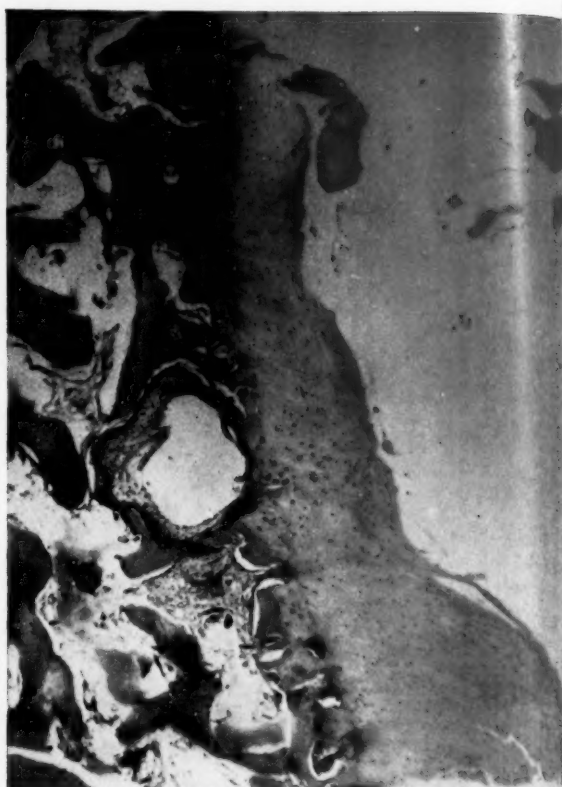


Fig. 5.—Case 2, posterior part of resected proximal end of left clavicle, showing destruction of cartilage, infero-external osteophyt and diffuse condensation of bone.

#### Ostéo-arthrite de l'articulation sterno-claviculaire

##### RÉSUMÉ

L'ostéo-arthrite de l'articulation sterno-claviculaire fut trouvée chez douze malades se plaignant de douleur dans cette région. Dans deux cas cette douleur fut si sévère et rebelle au traitement, qu'on procéda à la résection chirurgicale, avec un bon résultat. Il s'agissait de cas du début d'ostéo-arthrite chez des femmes âgées de 30 et 35 ans, respectivement. Le diagnostic fut confirmé à l'examen histologique.

Les données pathologiques chez ces douze malades furent renforcées par l'étude de 22 cas d'autopsie.

#### Osteoarthritis de la articulación esterno-clavicular

##### SUMARIO

La osteoarthritis de la articulación esterno-clavicular fué encontrada en doce enfermos manifestando dolor en esta región. En dos casos el dolor fué tan grave e intratable, que se procedió a la resección quirúrgica con buen resultado. Se trató de casos de osteoarthritis temprana en mujeres de 30 y 35 años de edad, respectivamente. El diagnóstico fué confirmado histológicamente.

Los datos patológicos en estos doce enfermos fueron reforzados por el estudio de 22 casos de autopsia.

# NUMERICAL METHOD OF EVALUATING THE STATUS OF RHEUMATOID ARTHRITIS\*

BY

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In the field of rheumatism, one of the most pressing needs is for a standardized, objective, and reliable index of the activity of rheumatoid arthritis which, while not taking into account all the manifold manifestations of the disease, will nevertheless provide a trustworthy guide both to its course in individual cases and to therapeutic responses in multi-clinic trials. In this paper we present a summary of our previous work on the development of a Systemic Index which, we believe, fulfills this function. We also give an outline of the Articular

Index by which various joint findings may be summed up numerically.

## Systemic Index

The time-honoured principle of using one measurable facet of a disease as a guide to its clinical course is illustrated in Fig. 1, which portrays the progressive trends towards "remission" or "cure" in cases of typhoid fever, diabetes mellitus, pernicious anaemia, and rheumatoid arthritis. The curves are based respectively on average daily temperature; fasting blood sugar; haemoglobin per cent., and the index of systemic activity. Naturally, these individual

items do not tell us about the structural changes wrought by the "activity" of the disease in question. Thus, we cannot tell from the fever chart alone that the typhoid fever patient is about to have an intestinal perforation; nor can we infer from the fasting blood sugar that the diabetic patient is suffering from diabetic neuritis or gangrene; nor does the haemoglobin level inform us that the pernicious anaemia patient is suffering from postero-lateral sclerosis of the spinal cord; nor can we infer from the Systemic Index the extent of crippling in a case of rheumatoid arthritis.

Nevertheless, despite their monosignificance, these measurable facets of the three non-rheumatic diseases are an indispensable guide to therapy and to the general trend of disease "activity".

\* Presented at the IX International Congress on Rheumatic Diseases at Toronto in June, 1957.

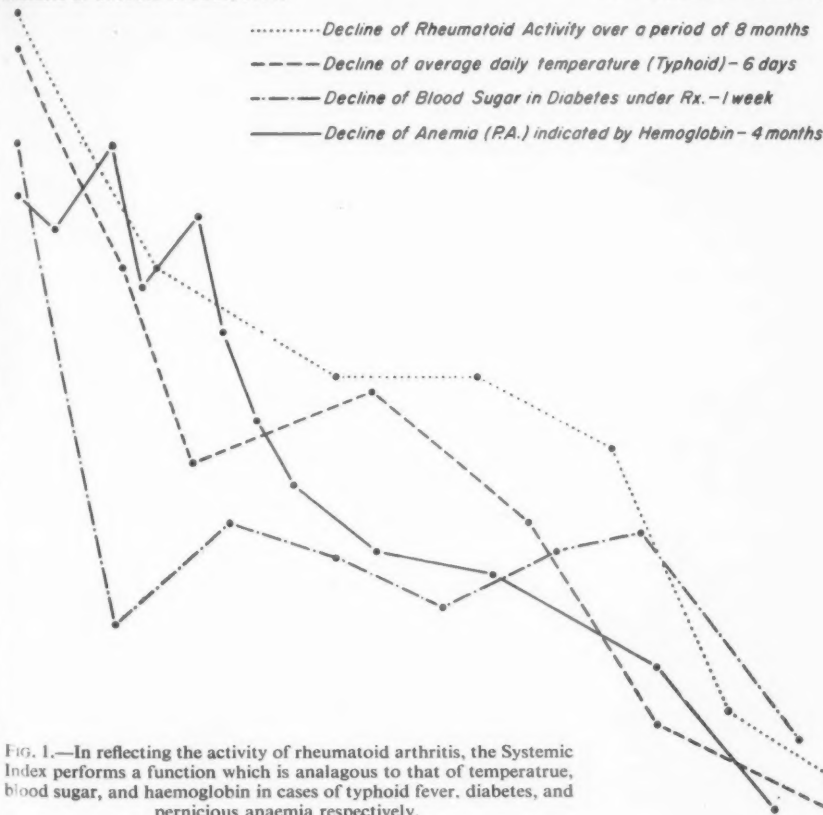


FIG. 1.—In reflecting the activity of rheumatoid arthritis, the Systemic Index performs a function which is analagous to that of temperature, blood sugar, and haemoglobin in cases of typhoid fever, diabetes, and pernicious anaemia respectively.



The Systemic Index, although composite, likewise serves as a guide to the activity of rheumatoid arthritis.

It has been objected that the Systemic Index cannot distinguish between a spontaneous and a drug-induced remission. But this is no argument against its usefulness, for such an objection applied to other diseases, would lead us to the ridiculous position of claiming, for instance, that blood sugar determinations are misleading in a case of diabetes mellitus because the vascular lesions may be slowly deteriorating despite the normalization of glucose values; or that the heart rate is not worth recording in a case of cardiac disease because, although controlled by digitalis, the underlying disease is getting progressively worse.

On the other hand, acceptance of the Systemic Index as a measure of "activity" in no way lessens the necessity for also observing slowly progressive structural changes. Indeed, where the inflammatory joint changes are themselves suppressed by powerful anti-inflammatory agents, the ultimate progress of the disease may have to be judged by serial x-rays, just as the slow advance of cardiac disease may be judged by the gradual enlargement of the cardiac silhouette as seen on the x-ray film.

The important thing is that the "activity" of the disease should be kept separate from the gross structural changes which are the result of that activity. (The present American Rheumatism Association classification was the first, we believe, to make this distinction.) In our scheme, the Systemic Index and the Articular Index keep these two aspects of the disease as separate as is possible.

#### Basis of the Systemic Index

(1) Separation of activity from deformity by relying only on systemic (non-articular) observations.

(2) Selection of those systemic manifestations which can be objectively and quantitatively observed and which are present in the great majority of cases at all stages of active disease.

(3) Summation of the values for each item by converting them to percentages of their average magnitudes in untreated patients.

Items meeting the above requirements are:

- (i) Duration of morning stiffness,
- (ii) Hours after rising before onset of fatigue,
- (iii) Number of aspirin tablets needed per day to control pain,
- (iv) Grip strength,
- (v) Erythrocyte sedimentation rate.

Other systemic manifestations such as fever, weight loss, anaemia, diurnal jelling after rest, and number of hours of rest and/or motion pain have not been used, either because they occur so infrequently that they would only dilute the values of the five chosen items, or because they cannot readily be referred to a normal base line. Many of them are nevertheless worth recording and could be used in a multi-clinic test of a drug where they could be mathematically treated at leisure.

The reader may at this point object that stiffness, fatigue, and aspirin consumption are purely subjective, but we may point out that patients are concerned with the *intensity* of their stiffness, fatigue, and pain but have no strong feelings about duration, time of onset, or number of tablets. Their statements are therefore unhampered by emotion and may thus be considered objective. Information gathered by two people, rather than one, is not automatically subjective or inaccurate.

We do not yet know in what way, to what extent, or how promptly each item reflects the activity of the disease, but we can be certain that, when any one of them definitely changes for better or for worse, the activity of the disease is also, in *this respect*, better or worse. A comprehensive statistical analysis by Mainland (1956) showed that no single index was highly correlated with any other, or with the average of the other four. This points to the desirability of using all five indices and to a need for discovering more indices, if possible. The real question seems to be not whether each index is accurate, but whether the five now in use constitute an adequate sample of the manifold manifestations of the disease.

Fig. 2 (opposite) shows, in an ideal fashion, the parallel manner in which the indices declined as a patient went into a full clinical remission. This parallel type of decline suggests that such quantitative data cannot be forced into artificial grades or categories or dealt with on a "yes or no", "present or absent" basis, and must therefore be dealt with by a process of averaging as noted below.

#### Method of Applying the Systemic Index

(1) *The Rubber Stamp*.—It is imperative that at each patient-visit *all five* items be recorded, since the omission of even one item invalidates the Index. To guard against such omissions a rubber stamp listing all five items is impressed on the patient's chart at the time of each monthly evaluation.

(2) *Duration of Morning Stiffness*.—One should never ask the patient "How long are you stiff in the morning", but rather "What time do you get up in

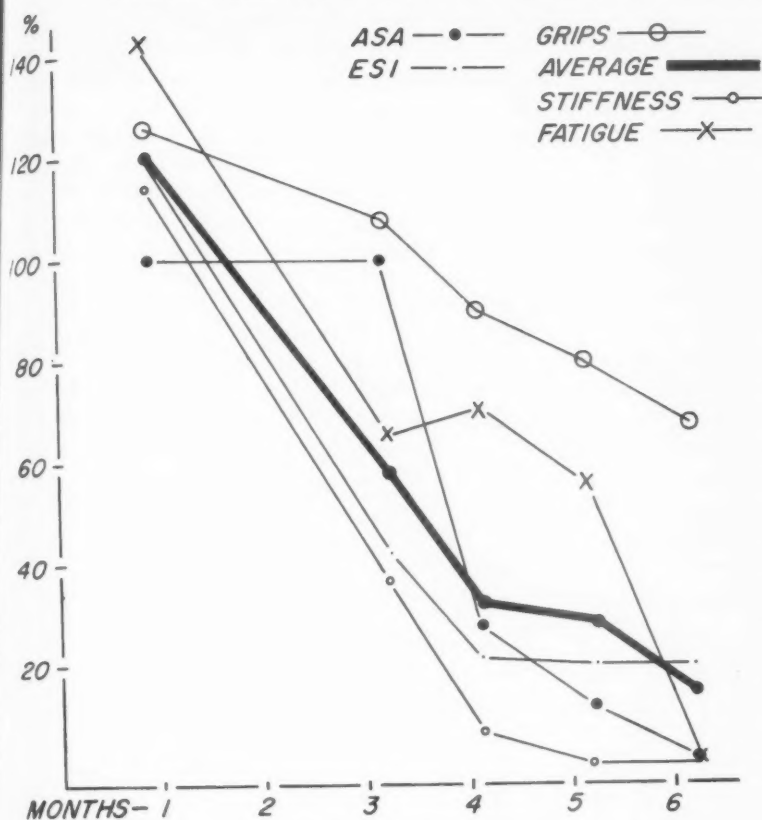


FIG. 2.—Items composing the Systemic Index decline in a more or less parallel fashion as the patient goes into remission, and are therefore dealt with by averaging rather than by assigning them to arbitrary grades.

the morning?", "Are you stiff?" If so, "By what time does the stiffness wear off", or "By what time do you limber up?" The observer then makes the calculation of hours of morning stiffness.

(3) *Hours after Rising before Onset of Fatigue.*—This is more difficult to elicit and some cross-questioning may be necessary. The hour of rising has already been established. One therefore asks "Are you tired when you get up in the morning?" If the answer is "Yes", this represents the maximum degree of fatigue, but one must immediately distinguish between neurotic fatigue, fatigue due to poor sleep, and true rheumatoid fatigue. Neurotic fatigue is a lack of desire for action and, in our experience, occurs infrequently in rheumatoid patients. Fatigue due to lack of sleep wears off in an hour or so, but fatigue due to rheumatoid arthritis does not. With this question settled, one then asks (if the patient is *not* fatigued on rising), "By what time of day do you feel tired?" It is important to distinguish between true fatigue and a desire to rest because of foot-pain.

(4) *Aspirin Required to relieve Pain.*—The patient should have at least one week's trial of a prescribed dose of aspirin, eight to twelve tablets per day, so that he may feel its benefit and not refuse to take it because it is "bad for the heart", etc. He is then instructed to take it *ad lib* for relief of pain. When near a remission, many patients take one or two aspirin tablets on retiring, as a sedative. This, naturally, does not count. One must also be sure that the patient is not taking aspirin just from habit, but such distinctions can easily be made by questioning the patient. Cohen and Calkins (1957) used a weekly record of the daily aspirin consumption and were favourably impressed by the accuracy of the average daily values.

(5) *Measurement of Grip Strength.*—For this we prefer an ordinary, rather than a pediatric blood-pressure cuff, and a standard mercury manometer blood-pressure apparatus which registers to 300 mm. Hg. The cuff is folded twice and the system inflated to 20 mm. Hg, the doctor then squeezes the bag and shows

the patient how to "ring the bell". With the mercury column in full view the patient then makes three tries to "beat the doctor". The highest reading for each hand is observed, and the average of the two recorded. In new patients it is well to try a fairly tightly-bound as well as a loosely-bound cuff, to be sure that one is not definitely superior to the other. Observations should be made at the same time of day. Where advanced deformities prevent an adequate grip on the cuff this item is rejected.

(6) *Erythrocyte Sedimentation Rate.*—We believe that the maximum fall of erythrocytes in any 5-minute period, as it occurs in the Cutler method over a 30-minute period, provides the best index of red cell sedimentation. Tentatively, we have also admitted the one hour reading by the Westergren method although a small study indicated considerably less uniformity in its results. (The Rourke-Ernstene method *should* give approximately the same information as the Cutler method. The Wintrobe erythrocyte sedimentation rate we have found quite unsatisfactory, as have many of our colleagues.)

(7) *Summation.*—The five items of basic information having been collected, the values are converted to percentages by referring to Table I. The sum of these is divided by the number of items (five, usually) to obtain the Systemic Index. The index should be charted on ordinary graph paper from month to month so that trends can be visualized.

(If one or more items are unobtainable, the average of the remainder may still be used as a guide to the course of the disease in individual patients, but the figure so obtained should not be regarded as being on the same scale as the full index of five components, and so should not be incorporated in a study of group responses to therapy.)

Summation is a key step in *any* process of evaluation because, either consciously or unconsciously,

it is always carried out no matter what method of evaluation is being used. Un-itemized and un-standardized types of summation used to classify activity into categories such as "very active", "moderately active", or "inactive", seem too poorly defined and too subjective to be used in collecting data from multiple observers. By comparison, the Systemic Index permits summation to be made in a standardized, objective manner.

Conclusions as to the Value of the Systemic Index

We have been using the Systemic Index for over 2 years and now have records of more than 2,000 observations on over 400 patient-visits. In more than thirty cases the Index has been charted in graphic form for periods ranging from a few months

TABLE I  
CONVERSION OF OBSERVED VALUES TO PERCENTAGE EQUIVALENTS

Duration of Morning Stiffness		Onset of Fatigue After Rising		Aspirin		Grip Weakness			Erythrocyte Sedimentation Rate			
						mm. Hg	Per cent.		Cutler		Westergren	
Min.	Per cent.	Hrs	Per cent.	Tab. per day	Per cent.		Male	Female	mm./5 min.	Per cent.	mm./hr	Per cent.
5	2	8.0	0	0	0	290	6	0	1.0	0	10	0
10	5	7.5	14	1	12	280	12	0	1.5	10	15	8
15	7	7.0	29	2	25	270	19	0	2.0	20	20	17
20	9	6.5	43	3	37	260	25	0	2.5	30	25	25
30	14	6.0	57	4	50	250	31	6	3.0	40	30	33
45	21	5.5	71	5	62	240	37	12	3.5	50	35	42
Hrs		5.0	86	6	75	230	44	19	4.0	60	40	50
1.0	29	4.5	100	7	87	220	50	25	4.5	70	45	58
1.5	43	4.0	114	8	100	210	56	31	5.0	80	50	67
2.0	57	3.5	129	9	112	200	62	37	5.5	90	55	75
2.5	72	3.0	143	10	125	190	69	44	6.0	100	60	83
3.0	86	2.5	157	11	137	180	75	50	6.5	110	65	92
3.5	100	2.0	171	12	150	170	81	56	7.0	120	70	100
4.0	114	1.5	186	13	162	160	87	62	7.5	130	75	108
4.5	129	1.0	200	14	175	150	94	69	8.0	140	80	117
5.0	143	0.5	214	15	187	140	100	75	8.5	150	85	125
5.5	157	0.0	229	16	200	130	106	81	9.0	160	90	133
6.0	171			17	212	120	112	87	9.5	170	95	142
6.5	186			18	225	110	119	94	10.0	180	100	150
7.0	200			19	237	100	125	100	10.5	190	105	158
7.5	214			20	250	90	131	106	11.0	200	110	167
8.0	229			21	262	80	137	112	11.5	210	115	175
				22	275	70	144	119	12.0	220	120	183
				23	287	60	150	125	12.5	230	125	192
				24	300	50	156	131	13.0	240	130	200
				25	312	40	162	137	13.5	250	135	208
						30	169	144	14.0	260	140	217
						20	175	150	14.5	270	145	225

Reprinted, by kind permission of Lea and Febiger from *The American Journal of the Medical Sciences*, 232, 305 (1956) with the following modifications: The percentage values for grips have been arranged so that it is no longer necessary to deduct the 20 mm. Hg used to inflate the cuff; haemoglobin values have been omitted.

SAMPLE CALCULATION

Items Observed	Date			
	July, 1956		March, 1957	
Duration of morning stiffness (hrs)	4.5	129%	0	0%
Onset of fatigue after rising (hrs)	3	143%	8	0%
Aspirin (tablets per day)	8	100%	0	0%
Average maximum grips (mm. Hg)	60	125%	200	37%
Maximum erythrocyte sedimentation rate (mm./5 min.)	7	120%	2	20%
SUM OF PERCENTAGES		617		57
SYSTEMIC INDEX (Divide Sum by 5)		123		11

to over 2 years (average 13 months). From these data we have drawn certain conclusions.

The method was applicable in about 90 per cent. of our patients. We feel certain that the Systemic Index, without joint findings, is capable of detecting a true clinical remission; moreover, it is a sensitive indicator, capable of registering values from 0 to over 200 per cent., thus detecting the widest swings in the activity of the disease.

When graphed at monthly intervals, the Index has proved a valuable guide to both treatment and prognosis and has permitted a study of exacerbating factors which would not otherwise have been detected. Fig. 3 illustrates the differences in trends of individual patients going into remission compared with those pursuing a more or less static course. From the point of view of accuracy, it seems to us that the Index compares more than favourably with other well-established procedures, such as, for instance, the basal metabolic rate in evaluating thyroid function. On the whole, patients

receiving steroid therapy register the most irregular courses. This is understandable, since a reduction of as little as 1.25 mg. meticorten per day may cause a significant rise in the Systemic Index.

Where the Systemic Index is used for drug testing in groups of patients, its various component items should be separately scrutinized, since a given drug might selectively affect certain items rather than all of them.

#### Articular Index

This is simply a device for estimating the total amount of arthritis. It is based on joint size as determined by the area of articulating surfaces. Its main use, so far, has been to sum up the extent of articular involvement without reference to degrees of joint inflammation or destruction, in other words, to express the "spread" of the disease. To use the Articular Index, one writes down the numerical value (instead of the name) of each affected joint as given in Table II (overleaf). The figures are added

and a decimal point is placed before the last digit. Since the total peripheral joint surface is approximately 1,000 cm<sup>2</sup>. (or 0.1 sq. m.), this gives the percentage of total possible joint involvement, and is the Articular Index. (For purposes of charting both indexes on the same graph paper, the articular index may be multiplied by a factor of 3 to bring it to a scale comparable with that of the Systemic Index.)

Theoretically Table II can be used to sum up a variety of joint findings. It is possible, for instance, to assess the amount of progressive destruction at yearly intervals as determined by x ray, provided satisfactory end-points can be agreed on. The Table has also been used to assess total lost motion in terms of "degrees lost per square centimetre of joint surface". This is a highly accurate but very

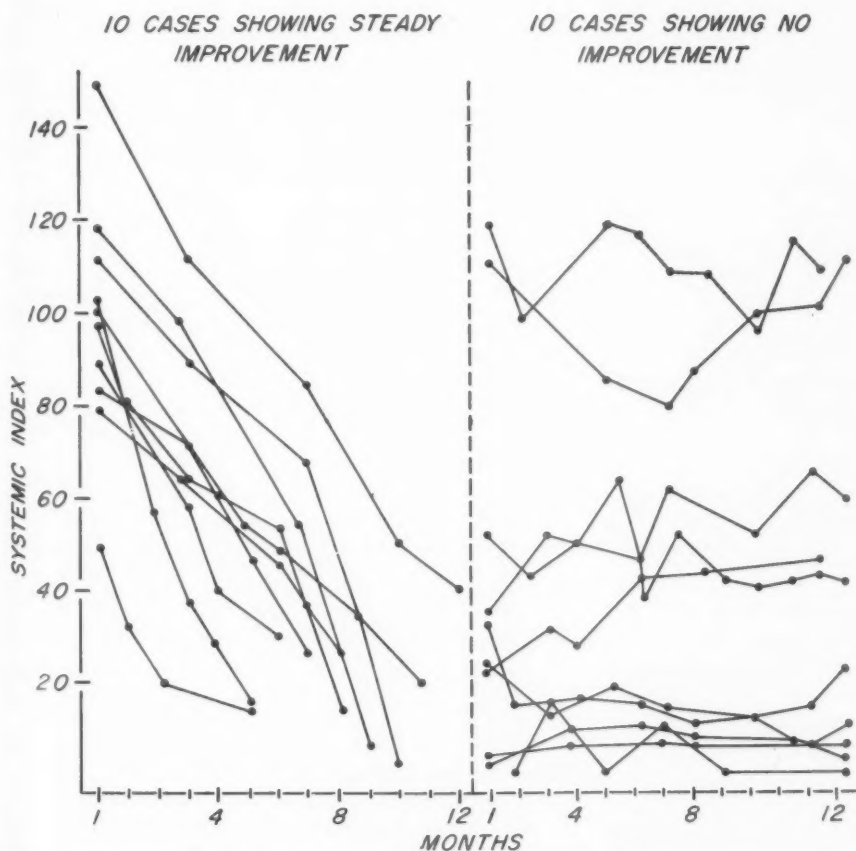


FIG. 3.—Two groups of ten cases of rheumatoid arthritis showing how the Systemic Index reflects the trends of activity. In each case the Index confirms the clinical impression of the observer. (Values of twenty or below would generally be classed as an excellent remission.)



TABLE II  
ARTICULAR INDEX  
PERIPHERAL JOINT SIZES EXPRESSED IN TERMS OF SQUARE CENTIMETRES  
OF ARTICULATING SURFACES  
TABLE FOR SUMMING UP JOINT FINDINGS

Joint	Size	Joint	Size
Each knuckle ..	4	Hips ..	82
First carpometacarpal ..	3	Knees ..	104
Wrists ..	15	Ankles ..	35
Carpal area ..	20	Subastragalar ..	18
Elbows ..	52	Talonavicular-calcaneo	
Shoulder ..	45	cuboid ..	21
Acromio-clavicular ..	4	Tarsal area ..	35
Sterno-clavicular ..	12	Bunion joint ..	8
Jaw ..	4	First proximal phalangeal	3
		Small toe joints ..	2

Reprinted, by kind permission of Lea and Febiger, from the *American Journal of the Medical Sciences*, 232, 152 (1956), with the following modifications: Finger and toe joints have been reduced to average figures of 4 and 1 respectively; carpal area now includes carpo-metacarpal joints; tarsal area now includes the tarso-metatarsals.

#### SAMPLE CALCULATION

Joints Involved	Size in cm. <sup>2</sup>
8 knuckles	32
2 carpal areas	40
1 wrist	15
2 elbows	104
1 knee	104
Total	295

Articular Index is Sum (295) divided by 10 = 29.5 per cent. = Percentage of total possible involvement.

tedious way of determining total articular function.\*

In determining the simple "spread" of the disease, we have, so far, used as our end-point any objectively observable evidence of clinically active arthritis irrespective of its intensity. This end-point perhaps needs to be more clearly defined. If gradations in joint "activity" can ever be accurately quantitated (which we doubt), the Articular Index may take its place with the Systemic Index as a measure of "activity".

Preliminary, retrospective studies of the present, simple Articular Index in relation to the Systemic Index have yielded some interesting results. A comparison between eighty random pairs of Systemic and Articular Indices indicated a fair correlation ( $r = 0.78$ ) as might be expected. Since the two indices measure quite different things, this is good supporting evidence for the accuracy of the Systemic Index through its full range of values. A subsequent comparison of charts showing the trends of both indices over long periods of time in fifteen patients has revealed a striking parallelism in ten cases.

\* Evaluation of total lost joint motion on eleven ambulatory patients in our clinic by Miss Emily E. Mueller, R.P.T., M.S., gave figures ranging from 30.3 to 53.0 per cent. While this agreed fairly well with our impression of the functional status of the patients, we did not feel that it justified the effort involved. Perhaps functional status is better gauged by qualitative methods.

These findings suggest that in some cases the overall activity of rheumatoid arthritis is well related to the total amount of inflamed joint tissue, irrespective of the degree of that inflammation. This may perhaps partly explain the difficulty experienced in trying to estimate the activity of the disease on the basis of grades of joint inflammation. A long-range, forward-going study of the relation of the Systemic Index and the Articular Index, with meticulous methods of joint evaluation, is needed to clarify this point.

The indices, when taken together, give us most of the information we need concerning a rheumatoid patient. However, they do not take into account certain very important items relating to the stage of the disease, such as local or general muscle atrophy, rheumatic nodules, etc. These are probably best kept in a separate category such as in the present American Rheumatism Association scheme.

#### Conclusions

In our hands the Systemic and Articular Indices have proved most useful in following the monthly progress of cases. But we do not as yet know the range of their applicability in other hands. We have therefore written this summary of our previous papers (Lansbury, 1956; Lansbury and Haut, 1956; Lansbury and Free, 1957), explaining them so that they can be more widely tested.

Pilot studies, using one or both indices as a drug-testing method, have already been completed by Bepler and Rogers (1957), Cohen and Calkins (1957), and Smyth and Clark (1957). Our indices were originally designed for drug-testing on a multi-clinic scale. The preliminary reports indicate that they are quite useful for this purpose.

We suggest that those who try the Systemic and Articular Indices should withhold judgment as to their value until they have used them for at least a year and have been able to see for themselves the strikingly different course of cases attaining a full clinical remission compared with cases in which the disease remains essentially unchanged. To be fully appreciated it is important to chart the indices month by month on ordinary graph paper.

Further studies needed in the field of evaluation include the following:

(1) Studies of inter-observer reliability in eliciting the items comprising the Systemic Index.

(2) Comparative studies of inter-observer reliability in grading joint inflammation. (This now constitutes the main basis for the present American Rheumatism Association grades of therapeutic response.)

(3) Improvement of the Systemic Index, particularly by weighting those items now in use. (We should be most grateful to receive serial data on patients going into a full clinical remission in order to make up the number of cases needed for weighting by statistical methods.)

No system for evaluating rheumatoid arthritis should be accepted merely because it is plausible. Its reliability should first be statistically determined and its practicability should be tested in many clinics, and preferably, in more than one country.

#### Summary

In this article the author sums up previously published accounts of the successive steps which have led to the introduction of the Systemic Index and the Articular Index as measures of the activity of the rheumatoid process and the extent of joint involvement. Explicit directions for applying these new methods of evaluation are given so that they can be more widely tested. The two indices, taken together, supply most of the information which is needed in dealing with rheumatoid patients, and, when graphed at monthly intervals, permit the progress of each case and the response to therapy to be seen at a glance. The indices have also proved useful in assessing therapeutic response in groups of patients and should therefore be well suited to trials of new drugs.

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#### Méthode numérique d'évaluer l'état de l'arthrite rhumatismale

##### RÉSUMÉ

Dans cet article l'auteur résume les travaux précédemment publiés concernant les étapes successives qui ont conduit à l'introduction de l'Indice Général (en anglais *systemic* = de l'organisme entier) et de l'Indice Articulaire comme mesures de l'activité du processus rhumatismal et de l'étendue de la lésion articulaire. On donne des instructions explicites pour appliquer ces nouvelles méthodes d'évaluation de façon qu'on puisse les essayer sur une plus grande échelle. Les deux indices, pris ensemble, fournissent la plus grande partie des renseignements dont on a besoin chez les malades rhumatismaux, et leur représentation graphique, de mois en mois, permet de se rendre compte d'un coup d'oeil des progrès de chaque cas et de leur réponse à la thérapie. Ces indices se sont aussi révélés utiles pour évaluer la réponse thérapeutique dans des groupes de malades et, par conséquent, ils devraient se prêter très bien à l'essai de nouveaux médicaments.

#### Método numérico para valorar el estado de la artritis reumatoide

##### SUMARIO

En este artículo el autor recapitula los trabajos publicados anteriormente respecto a los pasos sucesivos que condujeron a la introducción del Índice General (del organismo entero) y del Índice Articular como medidas de la actividad del proceso reumático y de la magnitud de la lesión articular. Se presentan instrucciones explícitas para aplicar estos nuevos métodos de valoración con el fin de facilitar su ensayo en mayor escala. Ambos índices, en conjunto, ofrecen la mayoría de los datos que se necesitan respecto a enfermos reumáticos y su representación gráfica, a intervalos de un mes, permite la observación fácil del progreso de cada caso y de su respuesta terapéutica. Estos índices revelaron también su utilidad en la valoración de la respuesta terapéutica en grupos de enfermos, se prestan pues a ensayos de nuevos medicamentos.

## EFFECT OF SALICYLATES ON THE CIRCULATING EOSINOPHILS AND URINARY 17-KETOSTEROIDS IN MAN

BY

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The anti-inflammatory and analgesic effects of salicylates have been observed for centuries, but their mode of action remains obscure. Their recommendation as the cheapest and often the safest medicament in rheumatoid arthritis (Ragan, 1949) and in rheumatic fever (McEwen, 1954; Coburn, 1943) has led to renewed efforts to discover how they work.

Salicylates and cortisone may act similarly in stimulating the pituitary to produce adrenocorticotropin, and subsequently in stimulating the adrenal cortex to increase its production of cortisone. Salicylates act like cortisone in some respects, but are totally unlike it in many effects (Hailman, 1952). The evidence for and against stimulation of the hypothalamus or the anterior pituitary by salicylate to produce an ACTH-like effect is conflicting and fragmentary (Smith, Gray, and Lunnon, 1954a, b; Bayliss and Steinbeck, 1953, 1954a, b; Meade and Smith, 1951; Shuman and Finestone, 1950; Feeney, Carló, and Smith, 1955; Done and Kelley, 1956; Marson, 1953; Cronheim, King, and Hyder, 1952, 1953; Cronheim and Hyder, 1954; Roskam and van Cauwenberge, 1951; Hetzel and Hine, 1951). The earlier studies suggested a salicylate effect *via* the pituitary-adrenal axis, but later reports discount this idea, since salicylates are able to exert their effect in the adrenalectomized animal (Ingle, 1941).

Two tests according evidence of anterior pituitary and, subsequently, adrenal cortex activation are in common use. Adrenocorticotrophic hormone in adequate doses indirectly and cortisone directly decrease the circulating eosinophils of the peripheral blood, while increasing the urinary excretion of ketosteroids. Most authorities approve of eosinopenia (the Thorn test) as a criterion of adrenal cortical stimulation (Thorn, Forsham, Prunty, and Hills, 1948; Shands and Bartter, 1952; Best, Kark, and Muehrcke, 1953).

*Effect on Eosinophils.*—A minimal depression of the circulating eosinophils (50-60 per cent.) is usually held to be necessary to establish a positive Thorn test. A distinction between the reaction of rheumatic and non-rheumatic individuals as regards eosinophil response and corticosteroid excretion has not been reported or, at least, the idea has not been accepted.

The published reports lack unanimity in describing the effect of salicylate upon the circulating eosinophils. Early studies indicated an eosinopenia following salicylate administration (Shuman and Finestone, 1950; Roskam and van Cauwenberge, 1951; Bertolani, Lorenzini, and Bonati, 1951), but recent workers have not confirmed this reported depression of the eosinophil count (McEwen, 1954; Meade and Smith, 1951; Marson, 1953; O'Connell, Roy, and Massell, 1955). It is suggested that the earlier results were due to the use of too large (*i.e.* toxic) doses of salicylate, so inducing a stress reaction (McEwen, 1954). According to Roskam and van Cauwenberge (1951), salicylates caused the eosinophils to decrease by 50 per cent. in 6 hours in rats. O'Connell and others (1955) found a salicylate potentiation of the eosinopenic effect of ACTH in humans; this was not interpreted as an effect upon the pituitary gland, but rather as a possible increase in peripheral utilization of the ACTH which was being given at the same time. Meade and Smith (1951) found that therapeutic doses produced no significant eosinopenia in 4 hours in humans. Lichtwitz (1944) again emphasized the distinction between the effects of therapeutic and toxic doses of salicylate in animal experiments.

*Withdrawal Phenomena.*—After withdrawal of steroids, the continuation by salicylate of the effects produced by doses of cortisone and adrenocorticotropin suggested that these drugs acted in a similar



manner. On the other hand, the marked relapses and disturbances which followed the withdrawal of steroids did not follow the withdrawal of salicylate. Salicylates were also synergistic in reinforcing the beneficial action of corticosteroids and ACTH in rheumatic fever (McEwen, 1954; Fischel, Frank, and McEwen, 1955; Fischel, Frank, and Ragan, 1952).

*Urinary 17-Ketosteroids.*—Evidence for increased 17-corticosteroid excretion following the administration of salicylate has been similarly conflicting. Steroids do bring about an increase in 17-ketosteroid excretion. Van Cauwenberge and Heusghem (1951) found that salicylate therapy regularly caused a rise in urinary adrenal corticosteroids, and said that it was apparent that each increase in the excretion of the reducing steroids corresponded with clinical improvement; temperature, erythrocyte sedimentation rate, and subjective symptoms all improved simultaneously. This suggests a similarity between the results of salicylate and cortisone therapy. At least three other groups of investigators, however, found that salicylate had no influence on the urinary excretion of adrenocortical steroids (Smith and others, 1954a; Bayliss and Steinbeck, 1954; Done and Kelley, 1956), and correspondingly, Norymberski, Stubbs, and West (1953) found no increase in the urinary ketosteroids. The explanation for the discrepancy in the findings has been the same: therapeutic doses do not raise the level of the 17-corticosteroids in the blood or urine, and toxic (too large) doses induce a non-specific stress effect.

*Cushing's Syndrome.*—Considering the frequency of Cushing's syndrome in patients treated with cortisone, Cochran, Watson, and Reid (1950) reported the development of a Cushing syndrome in a rheumatic fever patient treated with aspirin.

*Adrenal Ascorbic Acid and Cholesterol.*—Reduction of the content of ascorbic acid and cholesterol of the adrenal cortex is generally assumed to denote adrenal cortical activity mediated by ACTH (Feeney and others, 1955; Sayers, Sayers, Fry, White, and Long, 1944; Cronheim, King, and Hyder, 1952, 1953; Sayers, Sayers, Lewis, and Long, 1944; Rich, Berthrong, and Bennett, 1950). ACTH, as well as salicylates, has been found to deplete the ascorbic acid and cholesterol content of the adrenal glands in rats (Feeney and others, 1955). Hypophysectomy was found to prevent salicylates from reducing the ascorbic acid and cholesterol content of animal adrenals (Feeney and others, 1955; Sayers, Sayers, Lewis, and Long, 1944). On the other hand, however, some workers do not regard the reduction of ascorbic acid or cholesterol in the adrenal cortex

as specifically indicating adrenocorticoid stimulation.

Feeney and others (1955) proved that depletion of adrenal ascorbic acid and cholesterol are not criteria for the anti-rheumatic properties of a drug. The ascorbic acid depletion of the adrenal cortex has been attributed to the "stress" effect on the adrenal cortex (too large) doses of salicylates, rather than to a specific adrenocorticotrophic action (Smith and others, 1954; Norymberski and others, 1953; Sayers and others, 1944; Vogt, 1950; Roskam, van Cauwenberge, Vivario, and Vliers, 1955).

*Carbohydrate Metabolism.*—Several investigators have reported conflicting effects of salicylates upon carbohydrate metabolism, most agreeing that they increased blood sugar and glycosuria. Cortisone causes an increase in liver glycogen (Feeney and others, 1955; Ingle, 1950), while salicylates cause a fall in liver glycogen and reduce glycosuria in diabetic rats (Ingle, 1950).

*Peripheral Blood.*—In contrast with salicylates, cortisone tends to increase the erythrocytes and haemoglobin of the peripheral blood. Both cortisone and salicylates protect arteries against damage in experimental arteritis (Rich and others, 1950).

*Uricosuria, Hyaluronidase, and Erythrocyte Sedimentation Rate.*—Steroids and salicylates both increase uricosuria, lower the erythrocyte sedimentation rate, and have an anti-hyaluronidase effect. The metabolic changes following the administration of ACTH have been well summarized by Thorn, Prunty, and Forsham (1947), and the comparison of the metabolic effects of ACTH with those of salicylates have been summarized by Hailman (1952). The effects of steroids and salicylates are compared and contrasted in Table I.

TABLE I  
SIMILARITIES AND DISSIMILARITIES BETWEEN THE  
EFFECTS OF STEROIDS AND SALICYLATES

Results	Effects on	Steroids	Salicylates
Similar	Adrenal ascorbic acid	Decreased	Decreased
	Adrenal cholesterol	Decreased	Decreased
	Total lymphocytes	Decreased	Decreased
	Erythrocyte sedimentation rate	Decreased	Decreased
	Uricosuria	Increased	Increased
	Total eosinophils	Decreased	Decreased or unaffected
Dissimilar	Withdrawal phenomena	Present	Absent
	Haemoglobin	Increased	Unaffected
	Erythrocytes	Increased	Unaffected
	Urinary 17-ketosteroids	Increased	Reports conflict
	Liver glycogen	Increased	Decreased
	Hyaluronidase	Inhibited	Usually unaffected
	Cushing's syndrome	Induced	Usually absent



### Present Investigation

We have attempted to determine whether therapeutic doses of salicylates increase the production of adrenocorticotropin, directly stimulate the adrenal cortex, or have a cortisone-like action.

**Preliminary Study.**—This project has grown from a previous (unpublished) study carried out by Traut, Cech, and Stoker in 1946 of eight patients with severe (Grade III) rheumatoid arthritis in the West Suburban Hospital of Oak Park, in the Cook County Hospital, and in the Oak Forest Infirmary, Cook County, Illinois. In this study the eosinophils were counted before administering salicylates 1 or 2 g. daily orally or 4 to 8 g. daily intravenously, immediately after, 4 hours after, and daily for 7 days after salicylates were started. The peripheral eosinophils were also counted by the same group of workers in patients who had taken salicylates regularly for years. It appeared that salicylates, even in doses sufficiently large to produce tinnitus and nausea, did not depress the level of the circulating eosinophils in the majority of cases. The results are shown in Table II.

TABLE II  
EFFECT OF SODIUM SALICYLATE ON CIRCULATING EOSINOPHILS IN EIGHT PATIENTS WITH RHEUMATOID ARTHRITIS

UNPUBLISHED PRELIMINARY STUDY CARRIED OUT BY TRAUT, AND STOKER IN 1948

Case No.	Salicylates		Circulating Eosinophils	
	Dose (g./day)	Route	Before Treatment	After Seventh Day
1	3	Oral	62	76
2	2	Intravenous	300	481
3	2	Oral	219	306
4	4	Oral	119	112
	1	Intravenous	136	162
5	4	Oral	131	125
6	4	Oral	100	88
7	4	Oral	125	125
8	8	Oral	100	106

**Tests Employed.**—In the present investigation we have employed Thorn's test (depression of the circulating eosinophils; Thorn and others, 1948) and have also measured the urinary 17-corticosteroids after single and repeated doses of salicylates. The eosinophils were counted by the method of Pilot (1950), and the urinary ketosteroids were measured by the method of Archibald (1954).

**Material.**—We studied 43 female patients in the Cook County Hospital of Chicago. Fifteen of these patients had rheumatic disease, and 28 were non-rheumatic chosen at random.

**Method.**—The circulating eosinophils were counted before the study began, and 25 units of adrenocorticotrophic hormone were administered to determine the ability of these patients to react normally in producing corticosteroids with an oxygen atom on the 11 and 17 carbon positions (the so-called 11-oxysteroids and 17-oxysteroids). Acetyl-salicylic acid was then given orally to establish a therapeutic level. On the fourth day the circulating eosinophils were again measured, and the plasma salicylate level was determined in sixteen of the patients by the method of Brodie, Udenfriend, and Coburn (1944). On the eighth day of salicylate administration, the plasma salicylate level was measured in seventeen patients and the number of circulating eosinophils was determined in all the patients. The results in the 43 patients are shown in Table III (opposite).

**Results.**—In only four patients (7 per cent.) of the 43 tested (Nos. 11, 30, 33, 35 in Table III) did the circulating eosinophils decrease by 50 per cent. or more; one of these patients (No. 33 in Table III) had eosinophilia (amounting to 34 per cent. in the differential count) accompanying lymphogranuloma. In five patients (12 per cent.) the circulating eosinophils decreased by about 30 per cent. In 23 patients (54 per cent.) they decreased by less than 30 per cent. In eleven patients they were unaffected. These last plateau curves were obtained only in patients with rheumatoid arthritis (Table III).

In forty patients there was either an initial increase or a decrease after the third day of salicylates, the tendency being for the count on the eighth day to approximate to the initial count.

In eight patients (Nos. 36-43 to Table III), the enumeration of the circulating eosinophils was supplemented by a 24-hr determination of the urinary 17-ketosteroids before and after the administration of salicylates. The ketosteroid excretion increased by a negligible amount after the administration of salicylates for eight days. This increased excretion was not significant.

Thus, the number of circulating eosinophils fluctuated unevenly, but did not predominantly decrease. Neither did the urinary 17-ketosteroid excretion change in a manner characteristic of stimulation of the adrenal cortex.

### Summary

The number of circulating eosinophils was not usually significantly decreased (*i.e.*, by as much as 50 or 60 per cent.) by giving salicylates in therapeutic doses, and in some cases it actually increased. Nor did salicylates in full therapeutic doses increase the urinary excretion of 17-ketosteroids.

The initial increase or decrease in the eosinophils was followed by a return to the original count at the end of 8 days. In three exceptional patients

TABLE III

EFFECT OF SALICYLATE ON CIRCULATING EOSINOPHILS IN 43 PATIENTS, ON PLASMA SALICYLATE LEVELS IN 28 PATIENTS, AND ON URINARY EXCRETION OF 17-KETOSTEROIDS IN EIGHT PATIENTS

Case No.	Diagnosis	Oral Salicylates (g./day)	Circulating Eosinophils			Plasma Salicylate Level (Brodie)		Urinary 17-Ketosteroids* (mg./100 ml.)	
			Before Treatment	After 4th Day	After 8th Day	After 48 hrs	After 96 hrs	Before Treatment	After 8 Days
1		4	170	120	180	—	—	—	—
2		6	110	160	100	—	—	—	—
3		5	190	110	180	—	—	—	—
4		5	175	190	265	—	—	—	—
5		5	190	230	300	—	—	—	—
6		5	200	120	180	—	—	—	—
7		5	360	320	280	—	—	—	—
8	Rheumatic Fever	5	330	350	300	—	—	—	—
9	Rheumatic Fever	5	300	225	200	—	—	—	—
10		5.5	130	410	220	—	—	—	—
11		5.5	220	100	190	—	—	—	—
12		6	120	210	120	—	—	—	—
13	Rheumatic Fever	6	120	190	130	—	—	—	—
14	Rheumatic Fever	6	200	110	195	—	—	—	—
15		6	75	185	160	—	—	—	—
16	Lupus Erythematosus with Rheumatoid Arthritis	6	150	170	120	28.0	—	—	—
17		6	230	180	150	28.5	—	—	—
18		5	180	135	275	11.0	—	—	—
19		5	210	175	150	—	41.5	—	—
20	Salicylism	5	40	100	100	—	10.0	—	—
21		5	130	140	280	—	30.5	—	—
22		5	130	142	150	—	20.5	—	—
23		8	410	350	400	25.0	51.0	—	—
24	Degenerative Arthritis	6	230	150	160	17.5	40.0	—	—
25	Rheumatoid Arthritis	6	80	90	80	25.0	32.0	—	—
26		4	270	300	230	7.0	20.0	—	—
27	Pulmonary Fibrosis	5	650	760	220	8.0	25.5	—	—
28	Allergy, Obesity and Hypertension	5	640	440	410	14.0	16.0	—	—
29	Chronic Rheumatic Fever	5	250	200	130	6.0	13.0	—	—
30	Rheumatic Fever	6	260	130	200	21.5	44.0	—	—
31	Rheumatic Fever	6	200	110	100	21.5	30.0	—	—
32	Rheumatic Fever	6	410	500	400	26.0	30.0	—	—
33	Lymphogranuloma	6	1,730	800	660	27.0	30.5	—	—
34	Rheumatoid Arthritis	6	150	190	150	8.0	33.5	—	—
35	Suicide attempted with Aspirin	54 (toxic)	62	180	121	41.5	1.0	—	—
36		5.3	105	160	100	18.0	20.0	10.7	1.0

TABLE III—continued

Case No.	Diagnosis	Oral Salicylates (g./day)	Circulating Eosinophils			Plasma Salicylate Level (Brodie)		Urinary 17-Ketosteroids* (mg./100 ml.)	
			Before Treatment	After 4th Day	After 8th Day	After 48 hrs	After 96 hrs	Before Treatment	After 8 Days
37	Lupus Erythematosus	6.0	75	80	60	20.0	23.0	5.4	9.7
38		5.3	175	475	330	20.5	26.0	1.6	14.6
39	Rheumatoid Arthritis	6.6	80	120	270	17.0	21.5	3.0	4.3
40		8.0	110	140	110	17.0	32.5	10.7	8.8
41	Degenerative Arthritis	6.0	70	85	75	25.0	41.5	9.5	3.8
42		6.0	135	110	155	10.0	15.5	2.9	6.6
43		8.0	310	330	365	2.5	12.5	3.7	3.3

\* Normal value for urinary 17-ketosteroids in women is 4.6 to 13.4 mg./100 ml.

with an initial eosinophilia, the eosinophils decreased more than 50 per cent., but in the majority the response of the adrenal cortex to salicylates was slight.

One patient (Case 20 in Table III) showed symptoms of salicylism upon attaining a level of 10 mg. salicylate per 100 ml. plasma, and the eosinophil count in this patient actually rose during this episode.

In a programme of maximum salicylate administration, blood salicylate levels should be estimated frequently (Coburn, 1943). Mental disturbance, incontinence, tinnitus, headache, nausea, and vomiting should be given due importance.

The presumption of salicylate benefits mediated by the pituitary gland or adrenal cortex is not therefore acceptable in the light of our findings.

We should like to give credit to the following workers in this field of investigation: Dr. A. Dubin, Director of Biochemistry, Hektoen Institute and Cook County Hospital, Chicago (Brodie blood salicylate levels); Dr. D. MacFadyen, Director of Biochemistry, Presbyterian Hospital, Chicago (17-ketosteroid excretion determination by Dr. Hillyer's modification of the Archibald method); Dr. E. Chesrow, Director of Oak Forest Infirmary, Chicago.

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## L'effet des salicylates sur les éosinophiles sanguins et les 17-cétostéroïdes urinaires chez l'homme

## RÉSUMÉ

Des salicylates, en doses thérapeutiques, ne provoquaient pas généralement de chute appréciable (c'est-à-dire en dessous de 50 ou 60 pour cent) des éosinophiles sanguins et même, quelquefois, leur chiffre se trouvait augmenté. En fortes doses thérapeutiques, les salicylates n'ont pas, non plus, fait augmenter l'excrétion urinaire des 17-cétostéroïdes.

L'augmentation ou la diminution du chiffre des éosinophiles ne durait que 8 jours. Chez trois malades exceptionnels avec une éosinophilie initiale, le chiffre des éosinophiles baissa en dessous de 50%, mais dans la plupart des cas l'écorce surrénale ne réagissait que faiblement aux salicylates.

Un malade (No. 20 dans la Table III) acusa des symptômes de salicylisme au moment d'atteindre le taux de 10 mg. de salicylate par 100 c.c. de plasma; au cours de cet épisode le chiffre d'éosinophiles augmenta.

Quand on administre des doses maxima de salicylates, il faut déterminer souvent leur taux sanguin (Coburn, 1943), et considérer l'importance des désordres mentaux incontinence, tintement d'oreilles, céphalée, nausée et vomissement.

A la lumière de nos résultats on ne peut donc pas accepter l'hypothèse selon laquelle les effets favorables des salicylates seraient transmis par l'hypophyse ou l'écorce surrénale.

#### El efecto de los salicilatos sobre los eosinófilos circulantes y los 17-cetoesteroides urinarios en el hombre

##### SUMARIO

Los salicilatos, en dosis terapéuticas, no provocaban generalmente bajas significativas (es decir debajo de un 50 o 60 por ciento) de eosinófilos circulantes y hasta,

a veces, sus cifras se veían aumentadas. Con fuertes dosis terapéuticas los salicilatos tampoco hacían aumentar la excreción urinaria de los 17-cetoesteroides.

El aumento o la disminución de la tasa de eosinófilos no duraba más de 8 días. En tres enfermos excepcionales con una eosinofilia inicial, la cifra de los eosinófilos cayó debajo del 50%, pero en la mayoría de los casos la respuesta de la corteza suprarrenal a los salicilatos fué débil.

Un enfermo (No. 20 en el Cuadro III) acusó síntomas de salicilismo al alcanzar la tasa de 10 mg. de salicilato por 100 c.c. de plasma; durante este episodio su eosinofilia se vió aumentada.

Al administrar dosis maximas de salicilatos, hay que determinar su tasa sanguínea a menudo (Coburn, 1943) y atribuir importancia debida a desórdenes mentales, incontinencia, tintineo, cefalalgia, náusea y vómitos.

A la luz de nuestros resultados no se puede aceptar la hipótesis según la cual los efectos favorables de los salicilatos se transmiten por medio de la glándula pituitaria o la corteza suprarrenal.



## RHEUMATOID ARTHRITIS AND SYSTEMIC LUPUS ERYTHEMATOSUS

BY

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Kaposi (1872) first noticed the joint pains of lupus erythematosus and remarked that they might precede the acute stage of the disease. Osler (1904) and Jadassohn (1904) indicated the widespread visceral lesions and occasionally chronic nature of lupus erythematosus and referred to the occurrence of arthritis. Reifenstein, Reifenstein, and Reifenstein (1939) reported deforming arthritis indistinguishable from rheumatoid arthritis in three of eighteen cases of systemic lupus erythematosus (S.L.E.). The discovery of the L.E. cell phenomenon by Hargraves, Richmond, and Morton (1948) stimulated a new interest in the disease, which came to be diagnosed much more frequently, as the test appeared to be highly specific for S.L.E. The clinical picture thus acquired a new definition, though the evolution of the lesions was by now being modified by the use of cortisone. From 1953, reviews of large series of cases began to appear (Dubois, 1953; Ross and Wells, 1953; Harvey, Shulman, Tumulty, Conley, and Schoenrich, 1954). Dubois especially emphasized the frequency of arthritis as a presenting feature and remarked that "patients may complain of arthralgia with or without joint swelling for many years prior to any other evidence of systemic involvement".

The present paper describes 28 cases presenting the features of chronic rheumatoid arthritis in whom L.E. cells were demonstrated in the peripheral blood.

*Clinical Features.*—These are shown in Table I (opposite).

The average age at the onset of arthritis was 40 years (range 11 to 64). The longest duration of arthritis at the time of the first positive L.E. cell test was 26 years, but the longest period of observation from the first positive test is only 4 years. The arthritis in every case was typically rheumatoid, involving the hands, wrists, elbows, shoulders, ankles, and knees in every case; in fifteen cases the jaw joints and in six the hips were affected. In 22 patients the disease was advanced, with ulnar deviation of

the hands, disorganization of the wrists, and gross muscle wasting. In the remaining six cases, the fusiform swelling of the interphalangeal joints and effusions into the wrist, ankle, and knee joints were obvious. Subcutaneous nodules were constantly present in fifteen cases, of which four showed the characteristic necrobiotic histology. The systemic lesions listed in Table I occurred in fifteen patients, but in the other thirteen the arthritis was the sole manifestation throughout, and at the time of writing only two of the 26 surviving patients (Cases 8 and 24) show evidence of an active systemic lesion, in each case a progressive nephritis with renal failure. The laboratory findings are summarized in Table II (overleaf).

*Skin Lesions.*—Only three patients showed the classical erythema of butterfly distribution on the face. Recurrent urticaria was reported by two patients. In four patients (Cases 8, 9, 12, and 24), chronic ulceration of the lower limb of a peculiar character occurred. A painful nodular swelling in the skin broke down to form a shallow ulcer in which granulation tissue formed quickly. The area varied from 2 to 12" in diameter, and was on the thigh, leg, or dorsum of the foot. Healing was slow but complete and not obviously influenced by any form of treatment. Cases 8 and 12 have had one episode, each with two areas of ulceration, but Case 9 has had four separate attacks. In all four patients the arthritis was severe with gross deformity. These skin lesions are evidently the same as those recorded by Allison and Bettley (1957).

*Fatal Cases.*—Case 27, with chronic rheumatoid arthritis of 12 years' duration, was admitted to hospital with severe purpura, associated with thrombocytopenia, which responded fully to splenectomy after cortisone had failed to influence the platelet count. She died 6 months later from carcinomatosis secondary to a carcinoma of the rectum; the findings were confirmed at autopsy which revealed no characteristic lesions of S.L.E.

TABLE I  
CLINICAL FEATURES

Case No.	Age at Onset of Arthritis (yrs)	Duration of Arthritis at Discovery of L.E. Cells (yrs)	Systemic Manifestations (yrs after onset of arthritis)	Skin Manifestations	Nodules
1	37	7	Pleurisy (+7)	None	0
2	32	11	Pericarditis (+11)	None	0
3	58	0	Central retinal vein thrombosis (+2)	None	0
4	28	4	None	None	+
5	16	7	None	Urticaria	+
6	47	4	Pleurisy (+3)	None	0
7	11	26	Pericarditis (+7)	Urticaria	0
8	39	14	Nephritis (+8)	Leg ulcers	+
9	45	8	Pleurisy (+9)	Leg ulcers	+
10	35	20	None	None	0
11	52	13	None	None	0
12	64	7	Punctate keratitis (+6)	Leg ulcers	0
13	47	6	None	None	+
14	48	7	None	None	+
15	33	11	None	None	+
16	42	7	Staphylococcal septicaemia (+3)	None	+
17	28	3	Pericarditis (0)	Butterfly erythema	+
18	39	16	None	None	+
19	26	5	None	None	0
20	44	10	None	None	0
21	38	8	None	None	0
22	55	14	Nephritis (+14)	None	+
23	58	5	None	None	0
24	51	22	None	Leg ulcers	+
25	40	6	Pericarditis (+5)	None	+
26	30	24	Pleurisy (+24)	Butterfly erythema	+
27	57	12	Thrombocytopenia (+12) Carcinoma of rectum	None	0
28	30	10	Ovarian carcinoma	Butterfly erythema	+

Case 28, who had had severe rheumatoid arthritis for 11 years, developed ascites from a fixed ovarian growth and responded for 3 months to irradiation. She died in an institution but no autopsy was performed.

**Treatment.**—Twenty of the patients were given one or more 1-g. courses of Myocrisin. Ten considered that they had benefited, at least from the first course, and ten thought the treatment of no value. Four developed skin rashes and albuminuria attributable to the treatment.

25 patients were treated with oral cortisone, the daily dose not exceeding 100 mg.; five reported striking benefit to the arthritis, fourteen slight improvement, and six no change.

**L.E. Cell Test.**—All these patients gave a positive result on at least two occasions. In eighteen of them the test has at some later time been negative. 23 of the 28 cases had never received cortisone when the first positive result was obtained.

The method used was essentially that of Magath and Winkle (1952). 10 ml. blood are collected in a

TABLE II  
LABORATORY FINDINGS

Case No.	Highest and Lowest Erythrocyte Sedimentation Rate	Lowest Haemoglobin	Direct Coombs' Test	Sheep Cell Agglutination Test	Serum Proteins			
					Albumin	Globulin		
						$\alpha_1$	$\alpha_2$	$\gamma$
1	148/7	42	Pos.	—	2.5	2.75	0.56	1.5
2	78/26	78	Neg.	—	4.0	3.62	0.58	1.74
3	104/26	82	Neg.	—	3.42	3.68	0.58	1.88
4	6/1	72	Neg.	Neg.	4.13	3.89	0.61	1.85
5	108/35	66	Pos.	+++	2.9	4.4	0.6	2.3
6	84/44	86	—	—	3.76	4.24	0.58	2.61
7	64	91	Neg.	—	4.7	4.05	0.52	2.68
8	52/10	62	Neg.	+++	2.8	3.16	0.57	1.55
9	68/62	66	Neg.	+++	3.66	3.51	0.56	1.87
10	48/19	81	Neg.	+++	2.8	4.1	0.8	1.8
11	43/11	67	Neg.	+++	3.4	3.8	0.7	1.5
12	19	81	Neg.	+++	2.0	4.4	0.7	2.2
13	95/37	78	Pos.	+++	2.8	5.0	0.9	2.5
14	84/35	62	Neg.	+++	3.0	4.0	0.6	2.6
15	48/2	78	Neg.	+++	3.3	3.8	0.6	2.2
16	57	90	—	—	—	—	—	—
17	25/11	62	—	—	3.9	3.0	—	—
18	66	86	Neg.	+++	3.4	4.3	0.9	2.4
19	12/7	82	Neg.	++	2.8	4.3	0.8	2.1
20	32/18	86	Neg.	+	3.3	4.5	0.8	2.3
21	110/18	74	Neg.	+++	2.4	4.4	1.5	2.0
22	102/83	75	Neg.	—	1.3	3.8	1.0	0.9
23	73/40	80	—	+++	3.4	4.5	1.0	2.4
24	150/74	42	—	—	—	—	—	—
25	92/18	60	Neg.	+++	3.3	4.3	0.8	2.6
26	51/4	96	—	—	—	—	—	—
27	3	46	Neg.	+	2.74	2.4	—	—
28	76/64	56	Neg.	—	3.7	3.5	—	—

dry test tube, allowed to clot, and incubated for 2 hrs at 37° C. The serum is discarded and the clot is broken up with a glass rod by forcing it through a copper gauze sieve (40 strands to the inch) over a Petri dish. The material is pipetted into a Wintrobe tube and centrifuged at 2,000 r.p.m. for 5 minutes. The serum is withdrawn with a Pasteur pipette and discarded. Films are made of the buffy coat and are stained with Jenner Giemsa. About five slides of each preparation are made, and 15 to 20 minutes are spent examining each specimen.

The results of L.E. tests on 337 patients examined at Birmingham General Hospital are listed in

Table III (opposite). The series is not continuous and is not intended to indicate the relative frequency of the diseases included.

### Discussion

The concept of systemic lupus erythematosus as a disease with widespread manifestations not necessarily involving the skin, first suggested by Osler, has been greatly advanced by the discovery of the L.E. cell and the widely-held belief that it is specific for this disease only. Harvey and others (1954) found 79 positive tests in 96 cases of S.L.E. and

TABLE III  
RESULTS OF 337 L.E. CELL TESTS

Diagnosis	Result of Test	
	Positive	Negative
Systemic lupus erythematosus .. ..	9	0
Chronic discoid lupus erythematosus ..	0	8
Rheumatoid arthritis (including present series) .. ..	28	148
Polyarteritis nodosa .. ..	0	3
Scleroderma .. ..	0	4
Dermatomyositis .. ..	0	4
Rheumatic fever .. ..	0	16
Miscellaneous .. ..	0	117
Total .. ..	37	300

negative results in 553 other patients (including 116 cases of rheumatoid arthritis). Similar findings were recorded by Dubois (1953) and Haserick (1951). Positive tests in patients not considered to have S.L.E. have been reported in haemolytic anaemia (Lee, Michael, and Vural, 1951), miliary tuberculosis (Lee and others, 1951; Jacobs, 1955), rheumatoid arthritis (Slocumb, 1953; Bywaters, 1956; Thomas and Morgan, 1956; Kievits, Goslings, Schuit, and Hijmans, 1956; Ross and Clardy, 1956), chronic hepatitis (Joske and King, 1955; Mackay, Taft, and Cowling, 1956), pernicious anaemia in relapse (Berman, Axelrod, Goodman, and McClaughry, 1950), subacute glomerulonephritis (Parelhoff, 1953), and sensitivity to various agents including hydantoin (Miescher and Delacrétaz, 1953), penicillin (Walsh and Zimmerman, 1953), and hydralazine (Dustan, Taylor, Corcoran, and Page, 1954; Perry and Schroeder, 1954).

In most of these case records there are clinical features which suggest S.L.E. as a background to the presenting diagnosis. In the case of hydralazine sensitivity, the frequency of a clinical picture indistinguishable from S.L.E. must suggest the possibility that the drug may be an aetiological factor in this disease. No doubt some difficulty arises from a static morbid histological approach and an attempt to make a rigid definition of S.L.E. The point of unification of the apparently diverse cases mentioned above is the presence of a serum globulin capable of depolymerizing desoxyribose nucleic acid. If the primary stimulus is sufficiently strong and long-acting, the ultimate result is indistinguishable from S.L.E. whatever the initial mode of presentation. Within this definition we believe that the L.E. cell is specific for the condition S.L.E., always assuming that a sound technique is carefully interpreted.

Rheumatoid arthritis has long been recognized as more than a disease of the joints, so that the title "rheumatoid disease" has been proposed

(Sinclair and Cruickshank, 1956). The fever, rapid wasting, and malaise in acute cases, out of proportion to the severity of the arthritis, are suggestive of systemic disease, as are the subcutaneous nodules and the lesions occurring in muscle and nerve tissue (Freund, Steiner, Leichtentritt, and Price, 1942; Steiner, Freund, Leichtentritt, and Maun, 1946). Lung changes were reported by Ellman and Ball (1948) and specifically "rheumatoid" lesions in the heart have been described by Baggenstoss and Rosenberg (1944). Sokoloff (1953) found evidence of healed idiopathic pericarditis at autopsy seventeen times more often in patients with rheumatoid arthritis than in others, and Thomas and Morgan (1956) reported three cases of pericarditis in rheumatoid arthritis, of which two had L.E. cells in the blood. They did not regard these two patients as cases of S.L.E., and Kievits and others (1956), having found L.E. cells in 17 per cent. of 488 cases of rheumatoid arthritis, confined their observations to the difference in clinical features between the group with L.E. cells and that without them. The former showed a higher frequency of splenomegaly, disease of the lower respiratory tract, anaemia, and false positive serological tests for syphilis. Ross and Clardy (1956) analysed 91 cases of "rheumatoid-like" arthritis, of which eighteen had a positive L.E. cell test and revealed a considerably higher incidence of involvement of other systems than control groups with negative L.E. tests. Fifteen of our 28 patients had systemic lesions at some time in the course of their arthritis, in every instance compatible with a diagnosis of S.L.E. The remaining thirteen patients at no time had systemic manifestations. The average duration of arthritis in this group was 10.3 years and the greatest duration 22 years. The suggestion of S.L.E. would never have been made if L.E. cells had not been discovered on routine testing, as the whole clinical course was that of slowly advancing arthritis. Apart from the episodes of subacute illness, the group with systemic lesions has presented the same chronic picture. Case 7, for example, had fever and pericarditis 7 years after the onset of rheumatoid arthritis, which had been diagnosed as Still's disease at Great Ormond Street Hospital, but for the 19 years since that illness she had had no systemic disorder.

One cannot fail to be impressed by the tentative or negative conclusions of those writers who have found L.E. cells in cases which appeared to have classical rheumatoid arthritis. Thus Ross and Clardy (1956), who defined their cases with reference to the classification of the American Rheumatism Association (Steinbrocker, Traeger, and Batterman, 1949), still refer to "rheumatoid-like" arthritis and



so leave the significance of the positive L.E. test quite open. The same point is demonstrated in the admirable review of S.L.E. by Harvey and others (1954): on p. 319 it is stated that the arthritis in 28 of 95 patients with S.L.E. was described as typical of rheumatoid arthritis, while on p. 377 a Table records that 116 cases of rheumatoid arthritis were examined for L.E. cells without one positive result.

We may reasonably ask whether it is necessary to distinguish rheumatoid arthritis from S.L.E. Do these patients have S.L.E. with predominantly arthritic manifestations, or are they cases of rheumatoid arthritis with coincidental S.L.E., or of rheumatoid arthritis with unusual antibody formation giving rise to false positive L.E. tests? It seems to us best to regard them as cases of S.L.E. presenting as rheumatoid arthritis.

The further question, whether it is still necessary to consider rheumatoid arthritis a specific disease entity, cannot be answered here. The majority of cases of rheumatoid arthritis do not display visceral lesions suggestive of S.L.E. or L.E. cells in the blood, but this does not rule out the possibility that their condition represents a very chronic form of S.L.E. capable at times of becoming acute, though in many instances pursuing a chronic course throughout. Perhaps, then, rheumatoid arthritis will in the end be engulfed by the expanding empire of S.L.E., but, for clinical purposes at least, it remains a sufficiently distinct entity at present.

### Summary

28 cases of chronic rheumatoid arthritis with L.E. cells in the peripheral blood are reported. Systemic lesions suggestive of lupus erythematosus occurred in fifteen, and in three there was characteristic ulceration of the legs, but in thirteen arthritis was the only symptom. The significance of the L.E. cell test is discussed. The cases are considered to represent systemic lupus erythematosus with rheumatoid manifestations.

We wish to thank Drs. W. T. Cooke, W. C. Smallwood, B. C. Tate, and A. G. W. Whitfield for allowing us access to their patients.

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### L'arthrite rhumatismale et le lupus érythémateux généralisé

#### RÉSUMÉ

On décrit 28 cas d'arthrite rhumatismale chronique avec des cellules L.E. dans le sang périphérique. Dans 15 cas les lésions générales suggéraient le lupus érythémateux et dans trois autres cas les ulcérations des jambes en portaient le caractère, mais dans 13 cas l'arthrite en était le seul symptôme.

On discute l'importance de la recherche des cellules L.E. On croit que les cas décrit ci-dessus représentent le lupus érythémateux généralisé avec manifestations rhumatismales.

### La artritis reumatoide y el lupus eritematoso generalizado

#### SUMARIO

Se describen 28 casos de artritis reumatoide crónica con células L.E. en la sangre periférica. En 15 casos las lesiones generales sugirieron el lupus eritematoso y en tres otros casos hubo ulceraciones características de las piernas, pero en 13 casos la artritis fué la única manifestación.

Se discute la importancia de la búsqueda de las células L.E. Se considera que los casos descritos aquí representan el lupus eritematoso generalizado con manifestaciones reumáticas.

## BOOK REVIEWS

**Rheumatoid Arthritis.** By Charles L. Short, Walter Bauer, and William E. Reynolds. 1957. Pp. 480. Harvard University Press, Cambridge, Mass.; Oxford University Press, London. (55s.)

This book is undoubtedly a classic in the literature of the rheumatic diseases. It is based on a detailed study of 293 patients with rheumatoid arthritis, with clinical and laboratory data obtained according to a set plan, which was initiated in 1929 and which has been carried out with meticulous care. The previous literature is reviewed, pointing out that the term "rheumatoid arthritis" was introduced by Sir A. B. Garrod, and that his son, A. E. Garrod, published in 1890 a study of 500 cases, using control data, and giving figures for the frequency of a family history, the age and sex distribution, the aetiological significance of emotional disturbances and the influence of the menopause. The present study is a wider up-to-date record of the same type using modern methods of investigation.

In discussing the diagnostic criteria used, the authors have covered the differential diagnosis of the disease in a comprehensive manner. They admit the difficulty in some cases of a clear-cut distinction between the later changes of rheumatoid and degenerative arthritis. The inclusion in the series of cases of ankylosing spondylitis is explained, but will be regretted in this country where it is considered to be a separate disease. The known high familial incidence of this condition undoubtedly alters the figures in this series, though the authors state that no conclusion can yet be drawn as to the relative influence of environment, contagion or heredity. Careful analyses are made of the effect of other illnesses, operations, injuries, occupation, and the menopause, and are compared with control material. The mode of onset and constitutional symptoms have been studied in detail and the results are of the greatest interest. Laboratory investigations have been extensive and the findings are most valuable.

This detailed description of the disease by three distinguished clinicians from the Massachusetts General Hospital, backed by statistical evidence compared with a control series, is one of the most authoritative studies yet published. We are promised a further report on the life history of the disease and possibly one on rational treatment. These will be awaited eagerly by all physicians interested in rheumatoid arthritis.

OSWALD SAVAGE

**Cortisone Therapy.** By J. H. Glyn. 1957. Pp. 162, 4 figs. Heinemann, London. (21s.)

The author has had a long experience working with cortisone and its analogues, both in Great Britain and in the United States, and this book is the result of many years of clinical research in the field of rheumatic diseases.

There is a personal bias to some of the opinions expressed, but this makes the contents more readable and one is led pleasantly through the early years of experimentation with high dosage and alarming side-reaction to the present-day regime of treatment.

There is clear explanation of the chemical structure of steroids and useful Tables showing the different combinations which have such a confusing multiplicity of names.

The pharmacological properties are presented shortly and clearly and the side-effects are listed and discussed.

The author rightly emphasizes the importance of the most careful selection of cases for a treatment which may have to continue for a very long time, if not indefinitely.

The practical aspects of oral steroid therapy are dealt with in an excellent and authoritative manner.

Though the main part of the book is devoted to the use of cortisone in the rheumatic diseases, the other conditions in which these hormones may be used are described clearly with proposed schemes of dosage.

There are two appendices. The first, written by Dr. J. G. Bearn, gives practical advice on joint injections, and the second, by Dr. Glyn, gives suggestions for assessing the clinical progress of rheumatoid arthritis. This last section is the result of long practical experience.

This short book is thoroughly recommended for the practitioner who wishes to learn the simple rules of steroid therapy and for the student who receives an interesting introduction to this field.

OSWALD SAVAGE

**Rhumatologie Européenne. Revue critique de la littérature du 1 juillet, 1953, au 1 juillet, 1956.** 1957. Pp. 349. Secrétariat de la Ligue Européenne contre le Rhumatisme. L. J. Michotte (Sec. Gen. of Editorial Committee).

In a foreword, the President of the Ligue Européenne contre le Rhumatisme comments on the appearance of this publication which covers the relevant literature from July, 1953, to July, 1956. He points out that the *Annals of Internal Medicine* have already issued a number of excellent reviews of the rheumatic diseases but have unfortunately confined their attention to Anglo-Saxon literature. This volume represents an effort to redress the balance by placing emphasis on European bibliography—yet one more indication of the stresses to which the Atlantic Alliance is being subjected, for the Soviet workers, possibly to their own surprise, have been included in the company of good Europeans, and since some of them are bound to have Siberian addresses this unjustifiable annexation of the Northern portion of the Continent of Asia may have unpleasant repercussions in the neighbouring Chinese Peoples' Republic.

In dealing with such a mass of material, the editorial committee had to face the problem of classification without too much overlapping. Authors, for very good reasons, may call their paper "Low back pain" or "Lombalgia" and so it is only reasonable to find cervicobrachial and sciatic pain described both in the chapter on degenerative rheumatism (Chapter V) and in that on non-articular rheumatism (Chapter VII). The 349 pages are divided into nine chapters and sub-chapters, and the attempt at classification appears, on the whole, to have been successful. The difficulty of keeping a sense of balance under the circumstances is understandable but a word of criticism may be introduced here. In the sub-chapter on "Acroparaesthesia", for example, we are introduced to a mysterious state called the menopause, which, in this context at least, means only that the lady in question has suffered wear and tear. The concluding advice to the reader is worded as follows: "Il faut retenir que l'acroparaesthésie douloureuse nocturne paraît être l'expression, comme beaucoup de syndromes paroxystiques humains, de troubles essentiellement fonctionnels dont l'éclosion se fait ici sur terrain nerveux et de congestion veineuse surtout". Now French has always been regarded as the language

of diplomacy (which often means circumlocution), but why go to such lengths to avoid mentioning the carpal tunnel syndrome? In contrast, "Caplan's syndrome", a much rarer occurrence, finds a place of honour.

The Bibliography contains some 3,000 references, arranged at the end of each chapter. Although a Table of Contents is provided there is no Index, which is a pity.

DAVID FREISKEL

**A Osteo-Artrite do Joelho (Osteo-Arthritis of the Knee).** By Jacques Houli. 1956. Pp. 407, 60 figs. Companhia Brasileira de Artes Graficas, Rio de Janeiro.

This book covers everything one wants to know about osteo-arthritis of the knee. As is usual in the South American publications there is a full review of international opinion on each aspect of the subject under discussion. It is a pity, however, to find so many printing errors, especially in such important items as percentages, etc. There are ample illustrations and photographs and the bibliography is complete. This work was presented as a thesis for a chair of medicine in the University of Brazil, and as the author was successful the assessors must have thought highly of his effort.

PAUL B. WOOLLEY

## HEBERDEN SOCIETY

**Clinical Meeting.**—At a meeting held on December 13 and 14, 1957, at the Wellcome Foundation, the following papers were presented:

**Ulcerative Colitis and Arthritis.** By B. M. Ansell and E. G. L. Bywaters (*London*): All cases of definite ulcerative colitis attending Hammersmith Hospital and the Canadian Red Cross Hospital, Taplow, over the last 10 to 11 years have been reviewed for the presence of arthritis. The overall incidence of this complication appeared to be 15 per cent. 37 cases of arthritis with proved ulcerative colitis derived from this source and from cases seen at the Central Middlesex and West Middlesex Hospitals have been studied very closely.

The knee and ankle joints were most frequently involved and, in contrast to rheumatoid arthritis, the hand and tarsal joints were much less frequently affected. There was a relatively high incidence of sacro-iliac involvement, and of particular value diagnostically was the swelling of the proximal and distal phalangeal joints of the toes.

In most cases the arthritis was that of a recurrent mild synovitis, gross changes being found in only four cases, only two of which were typical of rheumatoid arthritis with nodule formation and a positive differential agglutination test.

The Rose test was repeated on a number of occasions in 29 patients; 25 were persistently negative, the two already cited persistently positive, and two others positive on one occasion only.

Eight of the 37 cases had erythema nodosum and this might occur early in the course of their disease or with an exacerbation. In seven of these the arthritis was present at the time of the erythema nodosum, and in one of these pericarditis was also seen.

On the basis of the frequency of the arthritis, its course and pattern, joint distribution, frequent association with erythema nodosum, and negative differential agglutination test, it is suggested that this is a separate arthritis from rheumatoid arthritis, either caused by the factor that produces the gut lesion or secondary to it. If it is indeed rheumatoid arthritis it has been considerably modified by the presence of ulcerative colitis.

**Rheumatoid Family Survey.** By J. S. Lawrence (*Manchester*): Parents, siblings, and children over 15 years of age of persons found to have either clinical rheumatoid arthritis or a positive sheep cell agglutination test in population studies at Leigh, Lancs., were submitted to a clinical and radiological examination and had blood taken for a sheep cell agglutination test, and the findings were analysed\*.

**Rheumatoid Arthritis of the Cervical Spine.** By J. Sharp, D. W. Purser, and J. S. Lawrence (*Manchester*): When x rays of the cervical spine of patients aged 55-64 years, who were suffering from rheumatoid arthritis, were compared with those of individuals in this age group selected at random from the general population, the

\* To be published in full in the next issue of this Journal.



features indicative of rheumatoid arthritis appeared to be narrowing of multiple disks, particularly the upper two, with relatively little osteophytosis of the vertebral bodies and a tendency to erosions rather than sclerosis of the adjacent plates, vertebral subluxation, particularly when occurring through narrowed disks or at multiple levels, and erosion of apophyseal joints.

Using these features as criteria, 427 radiographs taken from random samples of the general population in the age group 55-64 years were examined in an effort to recognize the subjects suffering from rheumatoid arthritis. The films were read without knowledge of the clinical or serological findings or of the radiological findings elsewhere.

The prevalence of these changes was found to be 6 per cent. in males and 7 per cent. in females in whom the changes tended to be more severe. On comparison with other criteria of rheumatoid arthritis in the population sample, it was found that the cervical changes were significantly associated with positive sheep cell agglutination tests and also with radiological changes of rheumatoid arthritis in the hands or feet but only poorly correlated with rheumatoid arthritis as diagnosed clinically. Both clinical rheumatoid arthritis and radiological changes of the disease in the hands or feet, however, showed a very significant association with positive sheep cell tests.

These findings suggest that in the general population a form of the disease may be encountered mainly or exclusively involving the spine, which is not diagnosed clinically as rheumatoid arthritis in the absence of changes of rheumatoid arthritis in peripheral joints. This form of the disease may be important in studies of the prevalence of rheumatoid arthritis in populations where it may account for some apparently "false" positive results in the sheep cell agglutination test.

In clinical practice, rheumatoid involvement of the cervical spine is important both on account of the associated pain, which may be severe, and the resultant mechanical instability which may result in severe cord damage.

**Pathology of the Rheumatoid Cervical Spine.** By J. Ball (*Manchester*): A characteristic feature of the intervertebral disks of the cervical spine is the presence of a synovial joint—the neuro-central joint—adjacent to their lateral borders. In a *post-mortem* study of twenty cervical spines from typical cases of rheumatoid arthritis (not selected on clinical or radiological grounds) neuro-central arthritis was found in all but one of the eighteen cases in which this area was examined; apophyseal joints were involved in nineteen; in neither was there a preferred site of involvement.

Disk lesions were frequently encountered, mainly in the postero-lateral and antero-lateral parts of the annulus and also along the disk-bone border in these regions. Serial sections indicated that the lesions were extensions of pannus arising in the roof or the anterior or posterior recesses of the neuro-central joint. In the affected area the annulus was replaced by granulation tissue varying in appearance according to the degree of maturation; the occurrence of bone in the postero-lateral part of the

annulus may represent a quiescent stage of a rheumatoid erosion and may be found in association with bony ankylosis of the corresponding neuro-central joint.

Atlanto-axial dislocation was found in three cases. Dislocation at the first, second, or third disk occurred in five cases, and in each instance there was associated erosion of the disk annulus posteriorly, anteriorly, or in both sites. Appreciable disk erosion is not necessarily accompanied by subluxation; occasionally this could be accounted for by ankylosis of the corresponding apophyseal or neuro-central joint.

In the single case in which dislocation was severe enough to cause compression of the cord, it was noted that some degree of fixation was present above and below the level of dislocation, mainly because of ankylosis of apophyseal joints.

The disk lesions found in the rheumatoid cases were not encountered in the cervical spines of twelve elderly subjects considered not to have suffered from polyarthritis. It was also noted that, whereas in the control cases disk narrowing and osteophytosis were predominantly located at the fourth and fifth disks, in the rheumatoid cases disk narrowing when present showed no such predilection for the lower disks and was often unaccompanied by conspicuous osteophytosis.

**An Operation to relieve Thoracic Rigidity in Ankylosing Spondylitis.** By C. E. Drew (*London*): A 55-year-old male suffering from a rigid thoracic cage following ankylosing spondylitis was referred by Dr. C. Foster Cooper. The patient complained of increasing dyspnoea which was now extreme and suffered repeated pulmonary infections. Respiratory function tests performed by Dr. L. H. Capel showed Vital Capacity=1,175 ml., one second FEV=1,175 ml.

The operation, which was carried out in two stages, consisted of the subperiosteal resection of  $\frac{3}{4}$ -in. rib segments posteriorly on both sides through incisions parallel to the spine. At the first stage segments were removed from ribs 1 to 5 and muscle placed between the rib ends. There were no post-operative complications. The improvement in pulmonary ventilation was immediate, accompanied by some return of ability to rotate the head and neck, which had been previously fixed.

Four months later the second stage was carried out, removing segments from ribs 6 to 10. On this occasion no muscle was placed between the rib ends. There was no immediate benefit, possibly because of interference with the fixed attachments of the diaphragm, but 18 months after the first operation the immediate improvement after the first stage had been maintained (Vital Capacity=1,920 ml., one second FEV=1,510 ml.). The patient had gained 3 stones in weight, and could walk for nearly a mile without dyspnoea; there was an upper chest expansion of  $1\frac{1}{2}$  in., and the head and neck movement was maintained. X-ray examination showed refusion of the lower ribs, but no fusion in the upper five ribs on each side.

**Heart Lesions in Rheumatoid Disease.** By B. Cruickshank (*Glasgow*): Previous workers have described a



variety of non-specific cardiac lesions in patients suffering from rheumatoid disease and the occurrence of rheumatoid granulomata in the heart is a well-recognized, though rare, occurrence. Most of the non-specific lesions have been regarded as of rheumatic aetiology. The whole picture is complicated by the inclusion of examples of ankylosing spondylitis in several of the previous series.

Heart lesions, other than those attributable to some other disease, have been studied in 100 patients suffering from rheumatoid disease. Rheumatoid granulomata were found in the mitral and aortic rings and cusps in five patients and in the myocardium in one of these. Active rheumatic heart disease was seen once and healed rheumatic endocarditis in five patients, in two of whom no histological examination was made. Non-specific chronic endocarditis was seen in nine patients. Although the macroscopic appearances suggested rheumatic endocarditis, microscopic examination failed to reveal characteristic lesions of that disease. In four of these patients the inflammation was active and diffuse, with many of the features found in rheumatoid lesions elsewhere in the body, though necrosis was absent. These are regarded as further examples of rheumatoid endocarditis. The other cardiac lesions encountered were myocarditis (10 patients), arteritis (20 patients), and pericarditis (15 patients), all of which occurred in a higher proportion of those admitted to hospital for treatment of rheumatoid disease than in those admitted for treatment of intercurrent disease. Many of these patients had extensive involvement of tissues other than the joints.

The incidence of rheumatic heart disease was no higher than in unselected autopsy series. It is considered that rheumatic fever plays no significant part in causing the cardiac lesions of rheumatoid disease and that many of these lesions are part of the rheumatoid process itself.

**Aortic Lesion of Ankylosing Spondylitis.** By E. G. L. Bywaters, B. M. Ansell, and I. Doniach (*London*): The aortic lesion of ankylosing spondylitis has been described by Clark, Kulka, and Bauer, in the U.S.A., but not in Great Britain. Two cases were found in a survey of 212 cases of ankylosing spondylitis followed to the present by Wilkinson and Bywaters. In one of these the disease started at the age of 22 with peripheral joint symptoms, later iritis and backache, sacro-iliac changes, and a rigid spine. The Rose test was negative and the erythrocyte sedimentation rate was raised. After 12 years, aortic incompetence developed with left ventricular enlargement and a prolonged P.R. interval. The Wasserman reaction, Kahn test, treponemal immobilization test, and Price precipitation reaction were all negative.

The second case was of a similar nature developing after 8 years. The patient died of heart failure, and a *post-mortem* examination revealed gross scarring resembling that caused by syphilis in the aorta down to the origin of the renal arteries, as well as valvular disease and incompetence. Again all serological tests for syphilis were negative.

**Observations of Plasma Ascorbic Acid, Plasma Dehydroascorbic Acid, and Plasma Caeruloplasmin in Rheumatoid Arthritis.** By Malcolm Thompson (*Newcastle-upon-Tyne*): Using a modification of the method of Roe and Keuther, estimations were made of plasma ascorbic acid (A.A.) and plasma dehydroascorbic acid (D.H.A.) levels in a series of patients suffering from rheumatoid arthritis, a series of healthy controls, and a group of patients suffering from various diseases. The results confirmed earlier observations that significantly low plasma ascorbic acid levels are found in rheumatoid arthritis. The values for plasma dehydroascorbic acid and the ratio D.H.A./D.H.A.+A.A. were shown to be within constant limits in normal subjects. The abnormalities found in rheumatoid subjects were compared with those found in patients with other diseases, especially inflammatory and neoplastic disorders and vitamin deficiency states. The results of short-term and long-term administration of ascorbic acid to patients suffering from rheumatoid arthritis were described and considered in respect of elevation of the plasma levels of ascorbic and dehydroascorbic acid, correction of the A.A./D.H.A. ratio, and effects upon the course of the illness and disease activity.

In view of work indicating that the metallo-enzyme caeruloplasmin was responsible for the oxidation of ascorbic to dehydroascorbic acid, estimations of plasma caeruloplasmin levels were made (using a method described by Scheinberg) in rheumatoid subjects, healthy controls, and patients suffering from various other diseases. Again, the normal range of plasma levels was defined and the significance of raised values found in rheumatoid subjects was considered in relation to the plasma levels found in those with various other disorders. The relationship between raised plasma levels of caeruloplasmin and abnormalities of ascorbic acid metabolism in rheumatoid arthritis was also studied. The effects of administering ascorbic acid and steroid compounds upon the plasma caeruloplasmin levels and upon capillary resistance were described and compared.

**Further Work on the Anti-Nuclear Serum Factor in Connective Tissue Disease.** By E. J. Holborow and D. M. Weir (*Taplow*): Sera from 100 cases of connective tissue disease have been examined by the fluorescein-conjugated anti-globulin test for the presence of the anti-nuclear factor previously described in disseminated lupus erythematosus (*Brit. med. J.*, 1957, 2, 732). Of eight cases of disseminated lupus erythematosus, seven were positive for both L.E. cells and the anti-nuclear factor, and one clinically typical, was negative in both tests. In three out of four doubtful cases of disseminated lupus erythematosus, the anti-nuclear factor was found. Of 44 sera from rheumatoid arthritis cases, eight contained the anti-nuclear factor. The L.E. cell test was positive in one of the latter (but the result of this test was available in only fourteen of the series). In Still's disease, three out of fifteen cases gave a positive anti-nuclear factor test; all were L.E.-cell negative.

Sera from the following cases were also investigated

with negative results: acute rheumatic fever, eleven; convalescent rheumatic fever, seven; polyarteritis nodosa, two; dermatomyositis, one; ankylosing spondylitis, one; and doubtful rheumatoid arthritis, five.

In the positive and negative rheumatoid arthritis group, comparisons were made between extent and activity of the arthritis, sex, age, duration, erythrocyte sedimentation rate, differential agglutination test, and nodules. Middle-aged females with a high differential agglutination test and nodules figure more commonly in the positive group. We have shown the affinity of the L.E. globulin factor for white cell nuclei of the rabbit, rat, mouse, guinea-pig, chicken, and toad, and in the chicken and toad the nucleated red cells also took up the factor. Tissue and white cell nuclei pre-treated with streptodornase failed to take up the factor.

Whether the anti-nuclear factor is responsible for the pathogenesis of L.E. remains in doubt; *in vivo* the factor is not taken up by the cell nuclei of tissues from L.E. cases; cell nuclei only take up the factor after *in vitro* incubation with the patient's own serum. Thus damage to the cell membrane or nuclear membrane seems to be an essential prerequisite for uptake of the serum factor.

**Treatment of Acute Rheumatic Fever with Phenylbutazone.** By G. Will (*Glasgow*): The treatment of 32 cases of acute rheumatic fever (nineteen males and thirteen females) was described, all of which fulfilled the modified Duckett Jones criteria. Seventeen cases were aged 16 years or under. In 21 patients it was the first known attack of rheumatic fever; eleven had been initially treated unsuccessfully with aspirin.

The maximum daily dosage of phenylbutazone was 600 mg.; this was given for the first few days and was followed by 400 mg. daily for 2 weeks, then 200 mg. daily for a further 2 weeks.

In every case there was a rapid response to treatment. Joint pain and swelling was relieved within 24 to 48 hrs and fever and tachycardia settled in 3 to 5 days. The erythrocyte sedimentation rate fell steadily to normal levels, in all cases to 15 mm./hr (Westergren) or below by the end of the fifth week of treatment. In two cases premature cessation of treatment was followed by relapse, with subsequent control on resuming treatment with phenylbutazone.

There was only one serious toxic episode in the series, a melaena. Mild epistaxis occurred in three cases.

## EMPIRE RHEUMATISM COUNCIL

### CHAIR OF RHEUMATOLOGY

The Empire Rheumatism Council has endowed a chair of rheumatology, which is being instituted by the Senate of the University of London at the Post-graduate Medical School of London at the Hammsmith Hospital.

Dr. E. G. L. Bywaters, senior lecturer at the Post-

graduate Medical School, has been appointed the first professor.

This is the second chair of rheumatology to be endowed by the Council, the first having been instituted at the University of Manchester in 1953.

## LIGUE EUROPÉENNE CONTRE LE RHUMATISME

### Fourth European Rheumatology Congress, 1959

At a meeting of the Bureau of the European League against Rheumatism it was decided that the next congress would be held in Istanbul from September 28-30, 1959.

Those wishing to make a communication to the congress should send in a summary to the Secretariat of the national committee in Turkey by April 1, 1959. A certain number of papers will be selected for the plenary sessions, and these speakers will be allotted

30 minutes; the remainder will be allowed 10 minutes.

A tour is being organized of 10 to 14 days by boat from Venice; this will include visits to the Aegean Islands with conducted tours and will allow 4 days at Istanbul covering the period of the congress. Particulars of this tour will be sent to all members of the Ligue Européenne, who are asked to indicate whether they are likely to be able to join it.

## C.M.A. AND B.M.A. JOINT MEETING, 1959

The joint meeting of the British Medical Association and Canadian Medical Association in July, 1959, will include a Section of Rheumatology which will hold one 24-hour afternoon session. The Canadian representatives are Dr. Arthur W. Bagnall (*C.M.A. Joint President*), Dr. Wallace Graham (*C.M.A. Vice-President*), Dr. Donald Graham (*Secretary*), and the B.M.A. representatives are Dr. George D. Kersley (*B.M.A. President*), Dr. J. J. R. Duthie (*B.M.A. Vice-President*),

and Drs R. J. G. Sinclair and John Glyn (*Secretaries*).

The meeting will consist of a symposium on "The Polyarticular Syndrome" by four speakers, a panel discussion on "Drugs in the Treatment of Rheumatoid Disease", and individual papers of 10 minutes each.

There will also be a Round Table Conference organized by the Canadian Medical Association on the subject of the rheumatic diseases.

## ABSTRACTS

This section of the ANNALS is published in collaboration with the two abstracting Journals, ABSTRACTS OF WORLD MEDICINE, and OPHTHALMIC LITERATURE, published by the British Medical Association.

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Pararheumatic (Collagen) Diseases; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with research into the scope and modus operandi of steroid therapy.

### Acute Rheumatism

**Further Studies on Rheumatic Fever Epidemiology. Comparative Incidence of Rheumatic Fever, Streptococcal Carriers, and Antistreptolysin Titres in the Tropics and in Mexico City.** SALAZAR MALLÉN, M., EVANS, M., and BALCÁZAR, J. (1957). *Amér. Heart J.*, 53, 767. 11 refs.

A previous investigation (*Ann. intern. Med.*, 1955, 42, 607) had shown that the ratio of rheumatic carditis to total heart disease (r/t index) was 0.5990 for hospital-referred patients in Mexico City, with a temperate climate, compared with 0.0967 for some tropical Mexican areas. The authors examined two groups of students, one from an area with a tropical and rainy climate and one from Mexico City with a more temperate environment. Throat swabs were plated on blood agar and colonies of  $\beta$ -haemolytic streptococci were grouped.

There was little difference in the incidence of Group-A  $\beta$ -haemolytic streptococci in the two groups (3 in 102 cases from the tropical region and 1 in 100 from the temperate climate). Nor did antistreptolysin-O titres show a significant difference; in fact, 55 per cent. of students in the tropical climate had a titre above 200 compared with 36 per cent. in the temperate region. Despite this, rheumatic fever was not found in the tropical group, but occurred in three out of 340 cases from the temperate area. [It is not clear how comparable these two groups were.] The authors suggest that a tropical climate affects the response of the host rather than the rheumatogenic agent.

E. G. L. Bywaters.

**Evolution of Rheumatic Fever with Antistreptococcal Treatment.** (Evolución de la fiebre reumática con tratamiento antiestreptocócico.) MENDOZA, F., CORREA-SUÁREZ, R., and CASELLAS, A. (1957). *Arch. Inst. Cardiol. Méx.*, 27, 25. 7 figs, 40 refs.

For the last 2 years all children with rheumatic fever admitted to the clinic of the National Cardiological Institute, Mexico, have been vigorously treated with large amounts of intramuscular crystalline and procaine penicillin initially for 10 days, followed by depot penicillin every 10 days thereafter. In addition tonsillectomy and other surgical procedures were performed when

clinically indicated, or when streptococci failed to be eradicated. The authors now report a retrospective study comparing the clinical course of the fifty children treated in this manner (Group 1) with the last fifty children treated before this antistreptococcal programme was established (Group 2). The two groups were well matched in regard to age, sex, number of first attacks, evidence of preceding streptococcal infection, duration of disease before admission, and initial severity of the disease. The last was judged on a composite grading system which took into account the visceral manifestations of rheumatic fever, other clinical manifestations of the disease, and also the results of a number of laboratory investigations.

In Group 1, the highest antistreptolysin-O titre (AS-O) was over 200 in 94 per cent. of the patients and fell to normal in 4 months in 52 per cent. In 33 of these tonsillectomy was performed and was followed by a transitory rise in the AS-O titre in nine. These nine were the only patients showing a secondary rise in AS-O titre, and the authors regard them as being probably the only cases in which tonsillectomy for the eradication of streptococci was required; comparable data for Group 2 were not available. The clinical outcome of the rheumatic fever in the two groups respectively was as follows: rheumatic process inactive within 4 months, 42 and 22 per cent.; within 5 to 6 months, 42 and 24 per cent.; within 7 to 9 months, 0 and 12 per cent. There were four deaths in Group 1 and twelve in Group 2. This more favourable outcome in Group 1 was supported by a radiological study of the heart size, which gave the following results: further enlargement, Group 1, nil, Group 2, 16 per cent.; smaller heart size 70 and 44 per cent. respectively. The figures for recovery from heart failure were also more satisfactory in Group 1 [but these are difficult to evaluate, as the results are given in percentages of the whole group and the actual numbers of patients in the two groups with heart failure before treatment are not given].

The authors conclude that adequate treatment of streptococcal infections shortens the duration of attacks and improves the outcome in rheumatic fever.

[This conclusion cannot logically be drawn from the



evidence presented, since alterations in the nature of the disease, or other factors, cannot be excluded as possible causes of the differences found between groups in this type of comparison. Nevertheless, it seems a reasonable working hypothesis.]  
Allan St. J. Dixon.

**C-reactive Protein in Rheumatic Fever.** (La C-réactive protéine dans le rhumatisme articulaire aigu.) RAHMAN, S., and MOZZICONACCI, P. (1957). *Sem. Hôp. Paris*, 33, 2179. 5 figs, 46 refs.

The authors studied 52 cases of rheumatic fever and thirteen of other similar diseases at the Hôpital des Enfants-Malades, Paris, comparing the erythrocyte sedimentation rate (E.S.R.) (Wintrobe method) and the serum mucoprotein (Winzler method) and C-reactive protein content (precipitin method described by Anderson and McCarty) before and during treatment with cortisone acetate or prednisone. After a reduction in the steroid dosage, aspirin was used, and during this period the C-reactive protein, which had disappeared rapidly with hormone treatment, reappeared in the blood in fifteen cases out of the 52 with rheumatic fever, together sometimes with a return of symptoms, sometimes with an increase in E.S.R. Four charts from individual cases and a figure summarizing all the results show that the serum C-reactive protein content falls rapidly after the start of hormone treatment; the E.S.R. falls less slowly and the serum mucoprotein content only very slowly.

The authors conclude that each of these tests is of value in following the course of rheumatic activity.

E. G. L. Bywaters.

**Prophylaxis of Relapse of Rheumatic Fever. Results in 377 Cases followed-up for 5 Years.** (Prophylaxie des rechutes de rhumatisme articulaire aigu. Résultats sur 377 enfants suivis depuis cinq ans.) LABESSE, J., DAGONET, Y., FIDELLE, J., FAURE, A., DEBETZ, J., and MOZZICONACCI, P. (1957). *Sem. Hôp. Paris*, 33, 2005. 1 fig., bibl.

Routine chemoprophylaxis with sulphadiazine or oral or intramuscular penicillin after an attack of rheumatic fever was prescribed in 377 consecutive cases in children admitted to the Clinique Médicale des Enfants, Paris, between 1951 and 1956. They were followed for an average of 2.3 years. Continuous prophylaxis was maintained in 200 cases for an average period of 18 months, in 167 cases there were interruptions lasting up to several years during an average observation period of 37 months, and ten patients took no drugs (average observation 36 months).

Previous authors have shown that chemoprophylaxis with sulphonamides reduces the annual rate of relapse by about 80 per cent. In this series there were only four relapses in 117 patient-years of observation (3.4 per cent. per year) among those given 1 g. sulphadiazine daily, a reduction of 83 per cent. Serious toxic complications were rare and agranulocytosis was not seen. The authors' experience with intermittent courses of oral benzylpenicillin in high dosage was unfavourable. With 200,000 units daily, the relapse rate in 154 patient-years was 3.9 per cent. per year (but some of the relapses

occurred when the patients forgot to take their tablets), while with double the dose the annual relapse rate in 73 patient-years was 2.7 per cent. The total results with continuous oral benzylpenicillin were thus much the same as with sulphadiazine, but as oral penicillin has no toxic side-effects it is preferable. With intramuscular benzathine penicillin in doses of 1.2 mega units every 28 days, good blood levels were maintained. The relapse rate was 1.5 per cent. per year for 199 patient-years of observation, but this method of prophylaxis may cause hypersensitivity reactions. Oral phenoxymethylpenicillin ("penicillin V") is now being tested.

When there is a particular risk of streptococcal infection, larger doses must be given. Of 72 instances of pharyngitis in this series, 56 were proven to be due to  $\beta$ -haemolytic streptococci, an incidence of 5.2 per cent. per year in children receiving continuous prophylaxis and 15.3 per cent. per year in children not given such prophylaxis. Of nineteen children who received "adequate" penicillin treatment for their streptococcal infection, three (15 per cent.) suffered a relapse of rheumatic fever, whereas of 53 who did not receive adequate treatment, 31 (58 per cent.) suffered a relapse.

John Lorber.

**Hormone Treatment of Rheumatic Fever. Results in 387 Cases.** (Traitement hormonal du rhumatisme articulaire aigu. Résultats sur 387 cas.) MOZZICONACCI, P., and CARAMANIAN, M. K. (1957). *Sem. Hôp. Paris*, 33, 1970, 3 refs.

Between 1951 and 1956, 387 children were treated with adrenocortical hormones for rheumatic fever at the Clinique Médicale des Enfants, Paris. The patients were between 2½ and 16 years of age, and the period of observation ranged from 6 months to 6 years. In 207 cases the child was suffering a first attack.

Cortisone was given by mouth in daily doses of 100 to 300 mg., depending on the age of the child and the speed with which the temperature became normal. Treatment was continued for at least 15 days and was in any case continued until the erythrocyte sedimentation rate fell below 20 mm. (presumably in one hour—method not stated). ACTH was used particularly at the beginning of the treatment in about one-half the dosage of cortisone. Enough aspirin was usually given for 15 to 20 days after the hormone treatment to maintain a serum salicylate level of 35 mg. per 100 ml. Penicillin was given continuously during the acute phase of the disease and subsequently.

There were 28 severe cases with pancarditis and cardiac failure, with seven deaths; eighteen of these 28 patients had had previous attacks and only twelve of these survived.

There were 221 children with carditis of moderate degree (including 117 relapsed cases). They all responded rapidly to treatment in respect of fever, arthritis, and skin lesions. In 155 cases the cardiac murmurs which existed on admission persisted unchanged, 38 children who had only systolic murmurs lost these during therapy, and 28 others lost some, but not all, of the murmurs which they had on admission. Patients



in their first attack more often showed improvement in the cardiac condition than those in relapse. In three cases new murmurs developed during treatment and persisted subsequently.

138 children without apparent carditis all recovered without developing cardiac lesions.

During the follow-up 328 patients suffered no cardiac relapse, 215 of these being observed for 3 years or more. Fresh attacks occurred in 39 cases, and in some the cardiac signs deteriorated. Of nineteen children treated for a first attack not associated with carditis who suffered one or more relapses, only one subsequently developed carditis. The cardiac status of six children deteriorated during the follow-up without apparent further attacks of rheumatic fever. Fourteen children died either during treatment or subsequently, four of them with bacterial endocarditis.

These results are compared with those of the combined Anglo-American investigation (*Brit. med. J.*, 1955, 1, 555; *Abstracts of World Medicine*, 1955, 18, 225).

(The analysis and interpretation of the results and their comparison with the Anglo-American results are made difficult by the apparent lack of a master plan governing the trial and by incomplete definition of the various criteria adopted and of the different types and grades of carditis and cardiac signs (in particular, systolic murmurs). Moreover, the calculation of the relapse rate and assessment of the final cardiac state suffer from the lack of standardization of the period of observation, no distinction being made between patients observed for 6 months and those observed for 6 years.)

John Lorber.

#### Hereditary and Environmental Factors in the Pathogenesis of Rheumatic Fever. DIAMOND, E. F. (1957). *Pediatrics*, 19, 908. 1 fig., 29 refs.

This paper from La Rabida Sanitarium, Chicago, reports a study of the families of 314 patients admitted with rheumatic fever during a 5-year period (1950-54). [It is stated that at this hospital "the average annual admissions for rheumatic fever number approximately 250", but it is not made clear on what bases the selection of cases for this investigation was made.] Multiple hospital and home interviews were carried out, the presence of rheumatic fever in relatives being ascertained by physical examination, study of hospital records, or, in "well known cases", by parental statements.

A comparison of 157 families in which one or both of the parents had a history of rheumatic fever with 157 in which the parents were apparently unaffected showed that there was a past or present history of rheumatic fever in 49 per cent. of the children in the former group as against 38 per cent. in the latter; when the index cases were excluded the figures were 31 and 16 per cent. respectively. This familial factor was shown much more clearly when 21 "positive-parent" families with four or five children were compared with 21 "negative-parent" families of the same size. Excluding the index cases the proportions of children with rheumatic fever in these two groups were 30 and 11 per cent. respectively.

The effect of environment was shown by dividing the

families into four groups on the basis of socio-economic, housing, and nutritional factors, those in the poorer groups containing a significantly higher proportion of children with rheumatic fever. However, in each of the groups there was a greater incidence in the families with a positive parental history.

The recessive-gene hypothesis of the transmission of susceptibility to rheumatic fever proposed by Wilson (1940) and Wilson and Schweitzer (1937, 1954) was tested by comparing the incidence of rheumatism in families of various mating types in which there was a positive rheumatic trait with that to be expected on the basis of the hypothesis. Agreement was obtained in families in which both parents had a positive personal or family history, but there was no agreement when only one parent had such a history.

E. G. L. Bywaters.

#### Histamine-fixing Power of Serum to Rheumatic Fever (Le pouvoir histaminopexique du sérum au cours du rhumatisme articulaire aigu.) PARROT, J. L., MOZZICONACCI, P., DANÉLATOS, C., and LABORDE, C. (1957). *Sem. Hôp. Paris*, 33, 2157. 4 refs.

Previous publications by some of the same authors has shown that human serum fixes or binds histamine *in vitro*, thus reducing its effect on the guinea-pig intestine (Parrot and others, *J. Physiol. (Paris)*, 1952, 44, 310), and that this property, which is enfeebled in various allergic states such as asthma, urticaria, eczema, and migraine, is also reduced in rheumatoid arthritis, gastro-duodenal ulcer, and tuberculosis (Parrot and Laborde, *Presse méd.*, 1953, 61, 1267; *Abstracts of World Medicine*, 1954, 15, 388).

The present study from the Hôpital des Enfants-Malades and the Hôpital Boucicaud, Paris, describes the investigation of sixty patients with rheumatic fever or a past history of an attack. The histamine-fixing power of the serum was abnormally low in all of 35 cases in the early stages of the disease, whereas it was normal in all but one of 25 cases in the healed phase.

E. G. L. Bywaters.

#### Determination of Blood Mucoprotein Levels in Acute Rheumatism. (Dosage des muco-protéines sanguines au cours du rhumatisme articulaire aigu.) LAGRUE, G., RAHMAN, S., and MOZZICONACCI, P. (1957). *Sem. Hôp. Paris*, 33, 2171. 4 figs, 12 refs.

The authors, using the Winzler method, have estimated the serum mucoprotein level in normal subjects and in patients with serious rheumatic states at the Hôpital des Enfants-Malades, Paris, and compared it with the erythrocyte sedimentation rate (E.S.R.) [presumably Westergren, but the method is not stated] and with the serum C-reactive protein content as an index of rheumatic activity.

In active rheumatic fever the serum mucoprotein level is increased, and it falls gradually with recovery. There is no very constant relation to the other two reactions, but in general an increased serum mucoprotein level is found over a longer period than the presence of C-reactive protein or a raised E.S.R.—in certain cases of chorea, Schönlein-Henoch purpura and erythema multi-

forme it was still increased although the other reactions were then normal. The authors conclude that this determination provides a simple and reliable method of following the evolution of rheumatic fever and a useful guide to treatment. E. G. L. Bywaters.

**Prevention of Secondary Attacks of Rheumatic Fever.** ZUKEL, W. J. (1957). *Publ. Hlth Rep. (Wash.)*, **72**, 895. 19 refs.

**Ultramicro-Determination of Salicylates in Blood Serum.** MACDONALD, R. P., PLOOMPUE, J., and KNIGHTS, E. M. (1957). *Pediatrics*, **20**, 515. 6 refs.

### Chronic Articular Rheumatism (Rheumatoid Arthritis)

**Relationship of Therapy with Cortisone to the Incidence of Vascular Lesions in Rheumatoid Arthritis.** KEMPER, J. W., BAGGENSTOSS, A. H., and SLOCUMB, C. H. (1957). *Ann. intern. Med.*, **46**, 831. 6 figs, 34 refs.

During the last few years the diagnosis of polyarteritis nodosa has been made clinically and confirmed histologically in an increasing number of patients suffering from rheumatoid arthritis. It has been suggested that the introduction of steroid therapy may have affected the incidence of these vascular lesions. The records of all patients with rheumatoid arthritis who died from any cause and came to necropsy at the Mayo Clinic during 1954 have therefore been examined. They totalled 52, fourteen of whom had received cortisone and 38 had not. Of the former group, four (29 per cent) showed generalized vascular lesions of polyarteritis nodosa, whereas none of those who did not receive cortisone showed any such lesion.

These findings suggest that certain susceptible patients with rheumatoid arthritis may develop diffuse arteritis following the administration of cortisone. The reason for this is not clear. No vascular lesions which could be considered specific for rheumatoid arthritis itself were found in any case. W. S. C. Copeman.

**Clinic and Prognosis of Rheumatoid Arthritis in Children.** [In English.] EDSTRÖM, G., and GEDDA, P. O. (1957). *Acta rheum. scand.*, **3**, 129. 12 figs, bibl.

The clinical course and prognosis in rheumatoid arthritis in children was studied at the University Hospital, Lund, Sweden, in 63 girls and 27 boys under the age of 15 years. In patients under the age of 12 years arthritis was first manifest in the large joints of the lower limbs; in older children the small joints were also attacked. Mono-arthritis was present in 27 cases, differential diagnosis in these cases being from tuberculous arthritis. Contractures occurred more often in children than in adults. During the initial phase of the illness the temperature was subnormal. Haematologically, there were hypochromic anaemia and eosinophilia, with an increase in the erythrocyte sedimentation rate. Subcutaneous nodules developed in five cases and

there were fourteen cases of peritendinitis. A few patients showed ocular changes, such as keratoconjunctivitis and iridocyclitis. Skin manifestations were common, ranging from a transient morbilliform rash to abnormal pigmentation. Five children were considered to be suffering from Still's disease, with pathological changes in the heart; the signs and symptoms in these cases included arthritis, fever, enlargement of the spleen and lymph nodes, sweating, wasting, and anaemia. One patient with Still's disease died from heart failure.

In the treatment of these cases every effort was made to avoid contractures by employing active movements, pin-traction, splints, and plaster-of-Paris bandages. Gold, salicylates, antihistamine drugs, and, especially in Still's disease, blood transfusions were given. When the patients were re-examined about 5 years later it was found that 53 children were free from symptoms. So far as the joint lesions were concerned, relapses were recorded in 29 instances.

The authors state that in spite of the increasing use of hormones in the treatment of rheumatoid arthritis in children there has been little or no improvement in prognosis. A. Garland.

**Rheumatoid Arthritis of the Crico-Arytenoid Joints.** COPEMAN, W. S. C. (1957). *Brit. med. J.*, **1**, 1398. 7 refs.

Rheumatoid arthritis of the crico-arytenoid joints is a rare condition, and although isolated cases have been described, mostly in Continental journals, and casual reference can be found to it in otorhinolaryngological text-books, the subject has hitherto received little attention. The present author describes three patients: a 60-year-old man and two women aged 54 and 70 years respectively. The chief symptom is hoarseness, without the development of sore throat, in a patient with rheumatoid arthritis. There is pain on coughing and swallowing. On direct laryngoscopy movement of one or both vocal cords is restricted and manipulation of the arytenoid cartilage with a spatula is painful. There may be redness or swelling about the cartilages. The episodes tend to recur and to coincide with a flare-up of arthritis in the peripheral joints. They are usually diagnosed as laryngitis and may be labelled hysterical until the true nature of the disease is known. In two of the author's cases the inflammation receded without leaving any permanent deformity, but in the third the cords remained fixed and hoarseness was permanent. William Hughes.

A further case of rheumatoid arthritis of the crico-arytenoid joints, with laryngeal stridor, is described by Baker and Bywaters in the same issue (*Brit. med. J.*, 1957, **1**, 1400).

**Observations on New Synthetic Antirheumatic Steroids and Critical Evaluation of Prednisone Therapy in Rheumatoid Arthritis.** BLACK, R. L., YIELDING, K. L. and BUNIM, J. J. (1957). *J. chron. Dis.*, **5**, 751. 1 fig., 21 refs.

Working at the National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland, the authors

have reviewed the therapeutic possibilities of certain new steroids in rheumatoid arthritis and have observed particularly the effect of long-term treatment with prednisone.

They point out that the advantages claimed for these substances are that they do not cause sodium retention and that they are effective in cases which have ceased to respond to cortisone. However, at the end of 2 years' observation of 39 patients treated with prednisone the number and seriousness of side-effects is causing concern. Pathological fractures occurred in 21 per cent. of cases, mental changes in 16 per cent., and peptic ulcer in 16 per cent. All the patients who developed severe side-effects were receiving a dosage of more than 15 mg. daily, and the authors conclude that the hazards of long-term treatment with prednisone increase markedly when the dosage is above this level.

Oswald Savage.

**Comparison of Cortisone and Prednisone in Treatment of Rheumatoid Arthritis.** A REPORT BY THE JOINT COMMITTEE OF THE MEDICAL RESEARCH COUNCIL AND NUFFIELD FOUNDATION ON CLINICAL TRIALS OF CORTISONE, ACTH, AND OTHER THERAPEUTIC MEASURES IN CHRONIC RHEUMATIC DISEASES (1957). *Brit. med. J.*, 2, 199.

Of 68 patients suffering from rheumatoid arthritis who had been treated with cortisone acetate at a number of centres in Great Britain for at least one year, 33 continued to receive cortisone, and 35, selected at random, received prednisone acetate in its place. A clinical assessment of each case was made on entry into the trial and repeated at monthly intervals for 12 months. The initial dosage of prednisone was one-third the dosage of cortisone previously taken, but adjustments were subsequently made to obtain the maximum possible benefit without side-effects. The average daily dose of cortisone was slightly more than 60 mg., whereas that of prednisone was about 20 mg. in the first few months, falling to 14 mg. by the end of the year.

On the whole the patients receiving prednisone required fewer analgesic tablets than those receiving cortisone. The cortisone group showed little change in clinical state at the end of the year, but the prednisone group had improved, on average, in respect of strength of grip, erythrocyte sedimentation rate, haemoglobin level, general functional capacity, and disease activity; the benefit from prednisone was greatest in the first 3 months and tended to decrease later, but this finding may be accounted for by the reduction in dosage to eliminate side-effects. On the other hand the incidence of "moon-face" was much higher in the prednisone-treated group.

D. Preiskel.

**Diagnosis, Treatment, and Prevention of Hypercortisonism in Patients with Rheumatoid Arthritis.** SLOCUMB, C. H., POLLEY, H. F., and WARD, L. E. (1957). *Proc. Mayo Clin.*, 32, 227. 3 figs, 28 refs.

In addition to the well-known effects of chronic over-dosage with cortisone or similar drugs, certain other

symptoms may occur, and it is with these latter "special" effects that this paper deals.

Such special effects seem to develop only in patients suffering from rheumatoid arthritis, when the usual signs of hypercortisonism have been present for some weeks. They are found most often in women after the menopause and least often in men. The smaller the daily dose of hormones, the later do these effects occur. The characteristic feature is a cyclic change of mood in which periods of "restless drive" and euphoria alternate with episodes of fatigue, aching, and emotional instability. Symptoms are worst when the time from the last dose is greatest, but increase in dosage accentuates the cyclic swing of symptoms and may complicate the course of symptoms arising from chronic hypercortisonism. Care is needed to distinguish such episodes from a flare-up of the underlying rheumatic process. In some cases features resembling disseminated lupus erythematosus or periarteritis nodosa develop; a number of such cases have proved fatal. In a comparison of 105 patients with rheumatoid arthritis who had not had hormones, 166 patients who had had hormone therapy without overdosage, and 128 patients suffering from chronic overdosage with hormones, the severity of the mesenchymal reactions, but not their incidence, was found to be greatest in the third group.

The recommended treatment of "special" effects of hormone therapy consists in adequate rest (at least 12 hours a day) and very gradual reduction in hormone dosage, with temporary increases if a flare-up of the rheumatism occurs. If possible all hormone therapy should eventually be stopped. Change of the type of steroid drug used has not shortened the time needed for recovery. The paper concludes with a review of the management of the general effects of hypercortisonism.

David Friedberg.

**Value of Chloroquine in Rheumatoid Disease. A Four-Year Study of Continuous Therapy.** BAGNALL, A. W. (1957). *Canad. med. Ass. J.*, 77, 182. 5 figs, 16 refs.

The author reviews his results obtained in the oral treatment with chloroquine of 125 patients [age unstated] seen in private practice in Vancouver who were suffering from "rheumatoid disease", under which heading he includes ankylosing spondylitis, psoriatic arthritis, and "cases of juvenile onset". The duration of the disease ranged from a few months to 6 years. Chloroquine was given in a dosage of 250 mg. daily, 75 per cent. of the patients receiving continuous therapy for more than a year and 50 per cent. for more than 2 years, the aim being to continue treatment for one year longer than the disease had been present. All patients were also receiving routine physiotherapy, planned rest, and sedation at the same time as chloroquine, as well as salicylates "in adequate dosage". Adrenal corticosteroids were given to 35 per cent. of the patients [doses and periods unstated] when the author considered them necessary. [There was no control group, although a small double-blindfold study (21 cases), too small for statistical analysis, showed that there was greater improvement in those given chloroquine.]



Routine clinical and laboratory examinations, of which a few details are given, were carried out before and at frequent intervals during therapy, but there were no facilities for performance of the Rose-Waaler test. Discussing the response to chloroquine the author points out that while some subjective improvement may result within a few weeks, objective response takes up to 12 weeks to appear and from 6 to 12 months to reach its maximum. By the standards of the American Rheumatism Association, remission or major improvement occurred in 70 per cent. of the patients, these gains being paralleled by improvement in work performance, erythrocyte sedimentation rate, and haemoglobin level. Of the 29 patients in whom the treatment failed, over half had had severe or prolonged rheumatoid activity, while the other half responded initially to chloroquine but suffered toxic side-effects necessitating reduction of dose or withdrawal of the drug. Toxic reactions, which are described in detail, included dermatitis (35 per cent. of all patients), nausea, vertigo and vomiting (32 per cent. of all patients), panleucopenia, and an unusual lymphoedema of the forearm and hand. These reactions were severe enough to require reduction in dosage in 36 per cent. of the patients, and permanent withdrawal in 10 per cent. Nevertheless, the author is of the opinion that chloroquine is one of the safest agents for the long-term control of rheumatoid activity and for the prevention of relapses.

J. Warwick Buckler.

**"Combined Medical Therapy" of Rheumatoid Arthritis, with Particular Reference to the Combination of Gold and Hormones.** (Considerazioni sulle cosiddette "terapie medicamentose associate" dell'artrite reumatoide, con particolare riguardo all'associazione crismo-ormonale.) ROBECCI, A. (1957). *Minerva med. (Torino)*, **48**, 2713.

**Prognosis in Rheumatoid Arthritis.** (Comment établir le pronostic thérapeutique dans la polyarthrite chronique évolutive (PCE).) FRANÇON, F., and FRANÇON, J. (1957). *Praxis*, **46**, 850.

**Contribution to the Study of Silico-Arthritis (Caplan-Colinet Syndrome).** (Contribucion al conocimiento de la silicoartritis (síndrome de Caplan-Colinet).) DI CARLO, F. C. (1957). *Rev. argent. Reum.*, **22**, 112. 7 refs.

**Arthritis of the Inferior Radiocubital Joint as an Early Sign of Rheumatoid Arthritis.** (Artritis de la articulación radio cubital inferior como signo precoz de la artritis reumatoidea.) CARUSO, A. C., and CEGORIAN-SKY, J. (1957). *Arch. argent. Reum.*, **20**, 19. 4 figs.

**Rheumatoid Arthritis with Onset in Old Age.** [In English.] OKA, M., and KYTILÄ, J. (1957). *Acta rheum. scand.*, **3**, 249. 7 refs.

**Still's Disease with Pseudoxanthoma Elasticum.** GOLD, S. C. (1957). *Proc. roy. Soc. Med.*, **50**, 473.

**Cervical Localization of Juvenile Rheumatoid Arthritis.** (Les localisations cervicales de la P.C.E. de l'enfant.) LE BAUDOUR, J. (1957). *Rhumatologie*, No. 2, 60. 7 figs, 15 refs.

**Management of Juvenile Rheumatoid Arthritis. The Problem of Long-Term Rehabilitation.** WILLIAMS, G. F. (1957). *Calif. Med.*, **87**, 244. 21 refs.

**Splenic Neutropenia in Felty's Syndrome.** BLAU, J. N., and WILLCOX, A. (1957). *Brit. med. J.*, **2**, 1094. 2 figs, 5 refs.

#### (Osteo-Arthritis)

**Spondylosis—a Disease of the Whole Organism.** (Spondylose—eine Erkrankung des ganzen Organismus.) STOIA, I., DRUGAN, A., ROSENTHAL, L., CĂLINESCU, J., and CONITZ, D. (1957). *Z. Rheumaforsch.*, **16**, 340. 27 refs.

**Radiculo-spinal Syndromes due to Cervical Spondyloarthrosis.** (A propósito de los síndromes radiculomédulares de etiología espóndilo-artrósica cervical.) BARRAQUER-FERRÉ, L., and VENDRELL, E. C. (1957). *Rev. esp. Reum.*, **7**, 249. 2 refs.

**Controlled Study of Prednisone, Aspirin, and a Placebo in Degenerative Joint Disease.** WILLIAMS, G. T., and WELCH, G. E. (1957). *Sth. med. J. (Bgham, Ala)*, **50**, 1063. 5 refs.

**Results of Local Hydrocortisone Therapy in 74 Cases of Osteo-Arthritis and Related Diseases.** (Resultate der lokalen Anwendung von Hydrocortison bei 74 Fällen von Arthrosen und verwandten Affektionen.) MEIER, F. (1957). *Praxis*, **46**, 811. 7 refs.

**Orthopaedic Treatment of Osteo-Arthritis of the Hip.** (Zur Orthopädie der Coxarthrose.) FRANCILLON, M. R. (1957). *Z. Rheumaforsch.*, **16**, 305. 8 figs, 67 refs.

**Significance and Frequency of the "Double-bottom" Sign in Radiographs of Osteoparthritic Hipjoints.** (Significato e frequenza del cosiddetto "doppio fondo" sintomo radiologico dell'artrosi coxo-femorale.) DI VITTORIO, S., and MONATERI, P. C. (1957). *Reumatismo*, **9**, 255. 9 figs.



## (Spondylitis)

**Ankylosing Spondylitis treated with Cortisone and Allied Substances.** CROFT, C. R. (1957). *Brit. med. J.*, 2, 137. 8 refs.

Experience of cortisone and allied substances in the treatment of fourteen patients suffering from ankylosing spondylitis is reported from the South Devon and East Cornwall Hospital, Plymouth. In the first five cases in the series, 10 to 25 units of long-acting corticotrophin (ACTH) was given twice daily, but later cortisone in a daily dosage of 50 to 100 mg. was employed. The duration of symptoms before the start of treatment varied from 1 to 40 years, but only in two cases was it under 5 years. Relief of pain was rapid and accompanied by some increased freedom of movement; this improvement was maintained when treatment was discontinued in two cases. One patient had marked relief of pain for 2 years while receiving corticotrophin, but died at the end of that period from cor pulmonale. Corticotrophin had to be discontinued in one case because of haemorrhage from a duodenal ulcer. Improvement was maintained in the two remaining patients, the period of observation ranging from 10 months to 2 years.

C. E. Quin.

**Value of Irradiation in Ankylosing Spondylitis.** HOWARD, N. (1957). *Brit. J. Radiol.*, 30, 371. 1 fig., 9 refs.

The author analyses the value of radiotherapy in the treatment of ankylosing spondylitis, bearing particularly in mind the genetic effects of such radiations and also the risks to the individual. The study is based on 455 out of 630 cases of the disease treated by irradiation at University College Hospital, London, between 1940 and 1953, all of which were followed up for at least 2 years, 31 per cent. being followed for up to 5 years, 38 per cent. up to 10 years, and 31 per cent. for over 10 years. The disease was regarded as typical in all but 28 cases and was divided into four stages radiologically. The patients were also grouped clinically according to their capacity for work. Treatment was in all cases given locally with conventional apparatus to a skin dose not exceeding 1,500r over 2 weeks to two fields.

Contrary to the findings in some published reports, leucopenia (less than 4,000 leucocytes per c.mm.) was found during or immediately after treatment in only eighteen of one hundred cases chosen at random. However, out of twenty women between the ages of 20 and 40 who had treatment to the sacro-iliac joints, in only five did menstruation continue unaltered. The number of patients of both sexes who received unavoidable radiation to the gonads was not considered large enough to be genetically significant, but the consequences for the individual patient are stressed. Attention is drawn to the relatively high incidence of pulmonary tuberculosis in patients with ankylosing spondylitis (twenty cases in this series), but there was no increase in the number of deaths from neoplasms. There were two cases of leukaemia, one of acute and one of chronic myeloid leukaemia, an incidence of 1 in 225.

Although 43 per cent. of the cases relapsed after the first course of treatment and had to undergo a second

course, the author finds that some 70 per cent. of these patients had derived considerable benefit from the treatment. The importance of general medical care and physiotherapy in conjunction with radiotherapy is stressed. The results in this series confirms that treatment by irradiation involves a tenfold risk of inducing leukaemia in these patients, compared with that in the general population.

R. D. S. Rhys-Lewis.

**Disorders of Liver Function in Rheumatic Diseases.** (Leberfunktionsstörungen bei rheumatischen Erkrankungen.) GROS, H. (1957). *Schweiz. med. Wschr.*, 87, 999. 10 refs.

**Lead Content of the Bones in Chronic Rheumatism.** (Blei in den Knochen von chronisch Rheumakranken.) JECKLIN, L. (1957). *Zbl. ArbMed. ArbSchutz*, 7, 213. 2 figs, 8 refs.

**Ochronotic Spondylosis.** (Espondilosis ocrónica.) BARCELÓ, P., and SANS SOLÁ, L. (1957). *Rev. esp. Reum.*, 7, 239. 3 figs, 13 refs.

**Calcified Tendinitis of the Shoulder.** FRIEDMAN, M. S. (1957). *Amer. J. Surg.*, 94, 56. 5 figs, 6 refs.

**Trigger Finger as a Rheumatic Manifestation.** [In English.] SAIRANEN, E. (1957). *Acta rheum. scand.*, 3, 266. 9 refs.

**Focal Infections and the Schönlein-Henoch Syndrome.** (Infezioni focali e sindrome di Schönlein-Henoch.) ORABONA, M. L., and SALONNA, L. (1957). *Policlinico, Sez. med.*, 64, 267. 9 figs.

**Ankylosing Spondylitis in Women localized initially to the Cervical Region and without Radiological Evidence of Sacro-iliac Involvement.** (Spondylarthrite ankylosante féminine à localisation initiale cervicale avec, à ce moment, intégrité radiographique des articulations sacro-iliaques.) GRABER-DUVERNAY, J. (1957). *Rhumatologie*, No. 2, 72. 4 figs, 12 refs.

**Crenotherapy of Ankylosing Spondylitis.** (Traitement crénotherapique de la spondylarthrite ankylosante.) BAGNÈRES, M. (1957). *Rhumatologie*, No. 3, 112.

**Diagnosis and Treatment of Ankylosing Spondylitis with a Special Study of Sacro-ileitis.** (Contribución al diagnóstico y tratamiento de la espondilo-artritis anquilopoyética con especial estudio de la sacro-ileitis.) RISEMBERG, A. (1957). *Rev. argent. Reum.*, 22, 152. 16 figs, 16 refs.

## (Miscellaneous)

**Pericarditis and Electrocardiographic Changes in Reiter's Syndrome.** CSOKKA, G. W., and OATES, J. K. (1957). *Brit. med. J.*, 1, 866. 8 figs, 13 refs.

The authors state that electrocardiography is now a routine procedure in their investigation of patients with Reiter's syndrome, and of a series of 24 such patients, three had an abnormal electrocardiogram (ECG).

In the first case, that of a man of 38, the ECG showed P-R interval of 0.28 second and ST elevation in leads I, VL, VI, V2, V3, and V4; 9 days later the patient complained of a pain in the chest, and a transient pericardial friction-rub was heard; the E.C.G. changes persisted for 6 months.

The second patient, a man of 24, had persistent tachycardia; the ECG in this case showed transient changes with elevated ST segments in leads I, II, CR1, CR4, and CR7.

The third patient, a man aged 33, complained of chest pain and had a pericardial friction-rub. The ECG showed ST elevation in leads I, II, V1, and V2.

The authors recommend careful assessment of cardiac status in all patients with Reiter's syndrome.

W. J. H. Butterfield.

**Reticulohistiocytosis (Lipoid Dermato-arthritis).** WARIN, R. P., EVANS, C. D., HEWITT, M., TAYLOR, A. L., PRICE, C. H. G., and MIDDLEMISS, J. H. (1957). *Brit. med. J.*, **1**, 1387. 7 figs, 18 refs.

**Aplastic Anaemia due to Phenylbutazone.** VENNING, G. R. (1957). *Brit. med. J.*, **2**, 146. 5 refs.

**Meprobamate (Miltown) in Rheumatic Diseases.** SMITH, R. T., HERMANN, I. F., KRON, K. M., and PEAK, W. P. (1957). *Amer. med. Ass.* **163**, 535. 5 figs, 4 refs.

**Periarthritis of the Shoulder and Tumour of the Lung.** (Periartrite della spalla e tumore polmonare.) BARBASO, E. (1957). *Reumatismo*, **9**, 176. 13 refs.

**Primary and Secondary Rheumatism with reference to Certain Cases of Polyarthritis with Pulmonary Tumours.** (Reumatismi primari e secondari con considerazioni su alcuni casi di poliartrite da tumore polmonare.) ROBECCHI, A. (1957). *Reumatismo*, **9**, 155.

**"Back to Work" Program for Physically Handicapped Arthritics.** MANHEIMER, R. H., and ACKER, M. (1957). *J. chron. Dis.*, **5**, 770. 5 figs, 3 refs.

**Rheumatic Manifestations in Hodgkin's Disease, Leukaemia, and Allied Conditions.** PAQUET, E., and DELAGE, J. M. (1957). *Canad. med. Ass. J.*, **76**, 927. 5 figs, 8 refs.

**X-Ray Therapy in Post-Traumatic Arthritis Pararthritis and Fasciitis.** STOLL, B. A. (1957). *Med. J. Aust.*, **1**, 868. 19 refs.

**Reversal of General Rheumatic Spread during Active Immobilization of Wrists.** [In English.] KELLY, M. (1957). *Acta rheum. scand.*, **3**, 203. 3 figs, 7 refs.

**Clinical Significance of the Serological Reactions in the Rheumatic Diseases.** (Die klinische Bedeutung der serologischen Reaktionen bei rheumatischen Erkrankungen.) SCHLEGEL, B., and BEHREND, T. (1957). *Z. Rheumaforsch.*, **16**, 182. 6 figs, bibl.

**Serological Reactions in Rheumatism.** (Serologische Reaktionen beim Rheumatismus.) HARTMANN, F. (1957). *Z. Rheumaforsch.*, **16**, 150. 8 figs, bibl.

**Surgical Treatment of Chronic Rheumatism.** (Traitement chirurgical du rhumatisme chronique.) WEBER, M. R. (1957). *Lille chir.*, **55**.

**Treatment of Post-Traumatic and Post-Operative Articular Rigidity with Hydrocortisone Acetate.** (Sul trattamento delle rigidità articolari post-traumatiche e post-operatorie con l'acetato di idrocortisone.) RUGGIERI, F., and CAPELLO, A. (1957). *Reumatismo*, **9**, 190. 25 refs.

**Experience with Phenylbutazone in the Treatment of 130 Cases of Rheumatism.** (Erfahrungen an 130 mit Phenylbutazon behandelten Rheumakranken.) STOIA, V. I., NITESCU, S., GRÜNWARD, L., and LEIBOVICI, S. (1957). *Z. Rheumaforsch.*, **16**, 146. 15 refs.

**Evaluation of Phenylbutazone (Butazolidin) in the Treatment of Gout, Rheumatoid Spondylitis, Rheumatoid Arthritis, and Other Conditions of the Musculoskeletal System.** TOONE, E. C., and IRBY, R. (1957). *Sth. med. J. (Bgham, Ala.)*, **50**, 655. Bibl.

**Ultimate Hormonological Basis of the Combination of Salicylates and Prednisone in Antirheumatic Treatment.** (Sull'eventuale substrato ormonologico dell'associazione salicilato-prednisone nella terapia antireumatica.) SCALABRINO, R., and PASQUARIELLO, G. (1957). *Reumatismo*, **9**, 180. 7 figs, bibl.

**Erythema Annulare Rheumaticum.** (Über das Erythema annulare rheumaticum.) GREITHER, A. (1957). *Arch. klin. exp. Derm.*, **204**, 205. 3 figs, 13 refs.

**Gastro-Intestinal Manifestations of the Schönlein-Henoch Syndrome. Roentgenological Findings.** HANDEL, J., and SCHWARTZ, S. (1957). *Amer. J. Roentgenol.*, **78**, 643. 7 figs, 17 refs.

**Incidence of Rheumatic Diseases.** (Indagini sulla diffusione delle malattie reumatiche.) ROBECCHI, A., BARBASO, E., DANEI, V., and MARRAZZI, G. (1957). *Reumatismo*, **9**, 209. 15 refs.

**Clinical Study of Patients with Rheumatic Diseases admitted to the S.N. Hospital, Agra, from 1946 to 1955.** GOUR, K. N. (1957). *Indian Heart J.*, **9**, 100.

**Aetiological Factor in Rheumatoid Arthritis and Rheumatic Fever.** (Poszukiwanie czynnika etiologicznego w gośćcu pierwotnie przewlekłym i w chorobie gośćcowej.) KWAŚNIEWSKI, S., WITOSZYŃSKI, S., ADAMSKI, J., and DOBEK, M. (1957). *Pol. Tyg. lek.*, **12**, 1101. 3 figs, 13 refs.

**Phenylbutazone as an Anti-Arthritic Agent.** VOLLMER, J., WEISKITTEL, R., and DE COURCY, J. L. (1957). *Ohio St. med. J.*, 53, 910. 18 refs.

**Uveitis in Association with Rheumatism.** HOGAN, M. J., THYGESON, P., and KIMURA, S. J. (1956). *Trans. Amer. ophthalm. Soc.*, 54, 93. 16 figs, 20 refs.

### Disk Syndrome

**Some Aspects of Cervical Spondylosis.** BRADSHAW, P. (1957). *Quart. J. Med.*, 26, 177. 2 figs, bibl.

A clinical study of 78 patients with cervical spondylosis and a neurological deficit was carried out at the General Infirmary at Leeds; males outnumbered females by four to one and the patients' ages varied from 28 to 68. In 55 cases myelopathy was present, sometimes with evidence of root lesions in addition, and in seventeen a radiculopathy was present. The average duration of symptoms was 2 to 3 years, during which time steady deterioration was usual. The mode of onset was: in 37 cases with symptoms of cervical root lesions—motor or sensory—with or without the later appearance of a progressive paraplegia; in nineteen cases with a progressive paraplegia without sensory disturbance, which might later be followed by involvement of the upper limbs; in five cases with simultaneous involvement of the upper and lower limbs; and in the remaining eight cases with completely atypical symptoms. One-third of the patients had cervical pain with or without radiation to the arms, 25 had brachial pain, and 41 had paraesthesiae most commonly affecting the distal portions of the upper limbs. Clumsiness of upper limb movement and stiffness of the lower limbs were the common motor symptoms.

Examination revealed occasional cranial-nerve abnormalities, and limitation of neck movement in forty patients. The motor signs included wasting, weakness, and fasciculation, with but slight spasticity, in the upper limbs, and in the lower limbs spasticity and disturbance of gait. Reflex abnormalities included extensor plantar responses in all cases of myelopathy, with exaggeration of the tendon reflexes in the lower limb, and absent abdominal reflexes in 50 per cent. In rather less than one-third of the cases abnormality of the reflexes in the upper limb suggested a cervical segmental lesion. The sensory impairment in some cases involved the peripheral parts of the dermatomes in the upper limbs, in others it resembled the suspended and dissociated sensory loss seen in syringomyelia in the lower cervical and upper dorsal dermatomes, and in a third group there was loss of sensibility below a well defined sensory level. Lumbar puncture showed a partial block in eight cases and a complete block in two fluid flow being normal in 61; in 22 cases the protein content of the cerebrospinal fluid was increased to 56 to 200 mg. per 100 ml. On plain radiography typical abnormalities were present in every case, varying in severity, and in all the 77 patients subjected to myelography anterior indentation of the column of opaque medium was present. However, the extent of the neurological disturbance bore little relationship to

the degree of abnormality seen on plain films of myelograms.

It is stressed not only that the features of a myelopathy attributable to cervical spondylosis may resemble those of other diseases, but also that the combination of cervical spondylosis and a neurological deficit does not afford assurance that the latter results from the former. Among conditions to be considered in differential diagnosis are motor neurone disease, disseminated sclerosis, subacute combined degeneration of the cord, and syringomyelia, as well as the various lesions outside the spinal canal which involve the motor and sensory innervation of the upper limb.

In considering the importance of trauma it is suggested that:

- (1) spondylosis localized to a single intervertebral level is indicative of a previous post-traumatic disk protrusion at this level;
- (2) in the presence of spondylosis trauma may aggravate an existing myelopathy without necessarily giving rise to a disk protrusion;
- (3) occupational stress does not appear to predispose to cervical spondylosis, though when the vertebral lesions are present it may increase the risk of a myelopathy developing.

Medical treatment was of little value in cases of myelopathy associated with generalized spondylosis, but improved most cases in which the spondylosis was localized, and relieved the majority of those with brachialgia. Surgical treatment carried a mortality of 10 per cent. There was initial improvement, but the disease frequently progressed again after 6 to 18 months—and among those cases in which good results were obtained are included those in which a protrusion of disk tissue had been excised, a procedure which is far more likely to benefit the patient than the laminectomy and division of slips of the dentate ligament which is alone possible in cases of true spondylosis.

It is pointed out that the aetiology of the myelopathy in cervical spondylosis is obscure, and stressed that it is seldom related to direct compression of the cord. Neither does tension applied through the dentate ligaments or constriction by adhesions appear to be responsible for the cord lesion. The possible importance of some mechanism interfering with the blood supply of the cervical cord is discussed.

[This paper is a valuable contribution to the literature dealing with cervical spondylosis.] J. E. A. O'Connell.

**Hypertrophic Osteosclerosis (Bony Spur) of the Lumbar Spine producing the Syndrome of Protruded Intervertebral Disk with Sciatic Pain.** SCHNITKER, M. T., and CURTZWILER, F. C. (1957). *J. Neurosurg.*, 14, 121. 3 figs, 14 refs.

Among a series of 154 patients operated on at St. Vincent's Hospital, Toledo, Ohio, for symptoms of prolapsed lumbar intervertebral disk (that is, backache and unilateral sciatica) nine were found to have instead a bony spur (localized hypertrophic osteosclerosis) which was compressing a nerve root. Of these nine patients eight were females and only one male, contrasting with a 2 : 1



male preponderance in cases of ordinary prolapsed disk. In seven of the cases the symptoms were precipitated by a fall on the buttocks, and it is postulated that a fracture or a periosteal tear at the interarticular isthmus with subsequent new bone formation may be an important factor in the aetiology. Pain was not as severe in onset as usually occurs in true herniation of a disk; the duration of symptoms was from 2 to 12 months. In four cases the patient complained of numbness in the involved extremity and two had paraesthesiae. Coughing and straining exacerbated the symptoms in four cases. Relief was obtained by three patients following rest in bed, and temporary relief by another three, but there was recurrence on mobilization. Physical examination showed no significant differences from the picture of prolapsed disk. Of interest was the fact that in eight cases the lesion occurred at the L4-L5 articulation, compressing the root of L5, while the remaining case was at L3-L4 involving the L4 nerve root.

Straight x-ray examination showed obliquity of the facets of the lateral intervertebral joint at the suspected level, and also a deformity which the authors term a "bulbous facet". The deformity may be verified by lumbar myelography in many instances. All nine cases were treated by unilateral hemilaminotomy. At operation the bony eburnation was found to arise from the medial margin of the facet or adjacent to the facet, that is, on the interarticular isthmus. Removal of the exostosis relieved the symptoms completely in eight of the nine cases. The authors regard the lesion as a manifestation of traumatic arthritis, and comment on the relief of back pain which followed operation in these cases, in contrast to its frequent persistence following operative removal of an intervertebral disk. *J. V. Crawford.*

**Low Back and Sciatic Pain.** BRADFORD, F. K. (1957). *J. Indiana med. Ass.*, 50, 559.

#### Gout

**Prevention of Attacks of Gout with Phenylbutazone.** (Prevención de los ataques gotosos por la fenilbutazona.) MORENO, A. R. (1956). *Arch. argent. Reum.*, 19, 188.

At the Anti-Rheumatism Centre of the Faculty of Medical Science, Buenos Aires, the author treated 22 men aged 42 to 70 with gout of 7 or more years' duration, each of whom had had four or more attacks in the preceding year, with 100 to 200 mg. phenylbutazone daily for 1 to 2 years. A similar group of 22 men with gout who received intermittent medication during attacks only served as controls. In addition, ten patients with gout were given continuous, then intermittent, then continuous medication in consecutive years.

Only seven attacks of gout occurred during the first year of the trial in the group of 22 men receiving phenylbutazone continuously, as opposed to 88 attacks in the control group. In the group receiving alternating methods of medication, the total number of attacks in the year before the trial was 47; in the first and third years (continuous medication) there were three attacks; and in the second year (intermittent medication) forty attacks.

No toxic effects were seen, routine leucocyte counts and urine examination being carried out. There was no effect on the hyperuricaemia. The author concludes that continuous treatment of gouty patients with small doses of phenylbutazone can safely be undertaken and will prevent recurrences of acute gout. [Data on the comparability of the treatment groups are not given.]

*Allan St. J. Dixon.*

**Changes in Serum Protein Fractions in Acute Attacks of Gout.** (Modifications des fractions protéiques sériques au cours de l'accès de goutte.) GROULADE, J., and JACQUELINE, F. (1957). *Rev. franç. Ét. clin. biol.*, 2, 345. 7 figs, bibl.

The serum of 45 patients presenting with various arthritic manifestations of gout has been analysed by zone electrophoresis for proteins, glycoproteins, and lipoproteins. Serial estimations were performed in five patients, four of whom had suffered exacerbations.

The serum of a gouty subject free of symptoms shows a slight diminution in the  $\alpha_2$  globulin and more pronounced of the corresponding glycoprotein, and an increase in the  $\beta$  globulin and, most strikingly, of the corresponding glyco- and lipo-proteins. Alterations in  $\gamma$  lipoproteins are related to the severity of the disease and even more to the diet. The onset of a relapse is heralded by a fall in albumin and  $\alpha_2$  glycoproteins and an increase in  $\beta$  and  $\gamma$  lipoproteins.

The usual concomitants of inflammatory reaction (increased  $\alpha_1$  and  $\gamma$  glycoprotein) are found but rather late in relation to the appearance of the clinical signs and their return to the previous levels is rapid.

Alterations in the differential protein pattern or in the sedimentation rate are marked only in severe exacerbations, suggesting a diminished ability of the body to react to the stimuli. The action of phenylbutazone, Benemid [probenecid], and colchicine on these changes has been studied.—[Authors' summary (transl. A. M. Jockes).]

**Phenylbutazone as a Presumptive Test for Acute Gout.**

**Preliminary Observations.** TROMMER, P. R. (1957). *J. Albert Einstein med. Cent.*, 5, 272. 11 refs.

**Current Status of the Treatment of Gout.** ROBINSON, W. D. (1957). *J. Amer. med. Ass.*, 164, 1670.

**Early Diagnosis in Gouty Arthritis.** GRAY, J. W. (1957). *J. med. Soc. N.J.*, 54, 374. 6 figs, 4 refs.

**Medical Treatment of Chronic Gout.** (Zur medikamentösen Behandlung der chronischen Gicht.) GAMP, A. (1957). *Ärzt. Wschr.*, 12, 779. 3 figs, 22 refs.

#### Pararheumatic (Collagen) Diseases

**Urinary Excretion of Creatine and Creatinine in Dermatomyositis.** CHRISTIANSON, H. B., O'LEARY, P. A., and POWER, M. H. (1956). *J. invest. Derm.*, 27, 431. 1 fig., 19 refs.

A study is reported from the Mayo Clinic of the urinary excretion of creatine and creatinine of 134 patients with dermatomyositis and 27 patients suffering from other diseases. Increased excretion of creatine



was observed in dermatomyositis, as well as in many other diseases, especially those characterized by muscular degeneration and wasting. Creatinuria is especially marked during the acute febrile stage of dermatomyositis. Remission of the disease, whether spontaneous or induced by administration of steroids, is accompanied by creatine. On the other hand, excretion of creatinine is reduced in all phases of dermatomyositis and in other diseases characterized by muscular degeneration.

The authors consider that the urinary excretion of creatine and creatinine is of limited value in the diagnosis and prognosis of dermatomyositis. *A. Swan.*

**Disseminated Lupus Erythematosus. A Clinical Study of Thirteen Cases.** (Le lupus érythémateux disséminé. Étude clinique de treize cas.) BONARD, E. C., JORNOD, J., and MULLER, A. F. (1957). *Rev. franç. Ét. clin. biol.*, 2, 262. 1 fig., bibl.

From the University Clinic, Geneva, comes this clinical account of thirteen cases of disseminated lupus erythematosus, twelve of which were in women. The prominent symptoms, in descending order of frequency, were fever, joint pains, pleurodynia and myalgia, loss of weight, and asthenia. The parts most commonly and most severely involved were the joints (ten cases), followed by the skin; the kidneys were the site of the presenting symptoms in only two cases and the heart in one. Poor resistance to infection was noted and was attributed to an abnormal plasma globulin pattern. The authors suggest that lupus erythematosus should be considered in the differential diagnosis of every case of pyrexia of uncertain origin, without waiting for a complete clinical picture to emerge. The multiplicity of the cutaneous manifestations is stressed and the inadequacy of the term "lupus" discussed.

In contrast to the variability of the clinical picture the disease, as a biological syndrome, is remarkably constant. It is characterized by a dysglobulinaemia with excess of globulins (usually of  $\gamma$  globulin and/or of  $\alpha_2$  globulin), and hypo-albuminaemia. The dysglobulinaemia is responsible for a number of abnormal laboratory findings, such as the raised erythrocyte sedimentation rate, abnormal plasma protein electrophoretic pattern, abnormal colloidal ("turbidity") test results, and false positive reactions in the Widal test and serological tests for syphilis. Among the abnormal globulins there may be a number of antibodies giving rise to haemolysis, leucopenia, thrombocytopenia, a positive reaction to the Coombs test, and, most important diagnostically, antinuclear bodies responsible for the appearance of L.E. cells. In all of the thirteen cases described the presence of L.E. cells was demonstrated. *A. Swan.*

**Six Years' Survival in Severe Systemic Lupus Erythematosus. An Analysis of Twelve Cases.** HASERICK, J. R. (1957). *A.M.A. Arch. Derm.*, 75, 706. 11 figs, 10 refs.

From the Cleveland Clinic Foundation, Cleveland, Ohio, are reported twelve cases (two in males and ten in females) of severe systemic lupus erythematosus in which the patients have lived six years or more after an acute episode from which they were not expected to recover.

Summaries of the case histories are given and photographs illustrate selected cases. Four of the patients originally came under observation following the discovery of false positive results of serological tests for syphilis. All twelve patients except one received steroid therapy during the acute phases of the disease, but the most dramatic therapeutic response was seen in two cases where steroids were combined with nitrogen mustard, although in one of these cases a severe leucopenia developed. Among adjuvant methods of treatment employed were x-irradiation of the ovaries (in three cases) and administration of antimalarial drugs. Such preparations were considered particularly useful as agents against photosensitivity and may have some value in reducing the dosage of steroids required for control. The author considers that steroid treatment is specifically indicated for acute episodes until a remission occurs, and that it may also be used during pregnancy or during surgical procedures to guard against possible untowards effects due to instability of the disease. Although it is recommended that pregnancy be avoided, it should be permitted to go to term when it does occur. During remissions in the cases reported L.E. tests, previously positive, became negative and serum protein electrophoretic patterns changed towards normal; even so it is suggested that although stable remissions may be obtainable it is doubtful whether true "cures" occur. *Benjamin Schwartz.*

**Lupus Erythematosus Syndrome: the Relationship of Discoid (Cutaneous) Lupus Erythematosus to Systemic (Disseminated) Lupus Erythematosus.** REICHES, A. J. (1957). *Ann. intern. Med.*, 46, 678. 19 refs.

The author has sought to elucidate the relationship between cutaneous and disseminated lupus erythematosus by means of a questionnaire sent to 1,200 Fellows of the American Academy of Dermatology, of whom 792 replied, and to 135 internists, one hundred of whom replied. By this method [which has obvious drawbacks] he has collected information about 353 cases of discoid lupus erythematosus known to have been followed by disseminated lupus erythematosus. Of the 353 cases L.E. cells were found in 97. It also appeared that the chronic localized discoid form of the disease often was present for many years before the development of the disseminated form.

Case histories are appended of three patients who had had chronic discoid lupus erythematosus for 13, 10, and 6 years, respectively, and who then developed the acute disseminated form of the disease. In all three cases L.E. cells were found together with leucopenia, thrombocytopenia, and reversal of the albumin : globulin ratio. Despite steroid therapy two of the three patients died shortly after the onset of disseminated lupus erythematosus. *J. N. Harris-Jones.*

**Sero-Diagnosis with Antigens of *Treponema pallidum* in Lupus Erythematosus.** REIN, C. R., CHARGIN, L., and KELCEC, L. C. (1957). *A.M.A. Arch. Derm.*, 75, 230. 17 refs.

Following upon the work of Moore on the biologic false positive reaction for syphilis in systemic lupus

erythematosus (*Ann. intern. Med.*, 1952, 37, 1156; *J. chron. Dis.*, 1955, 1, 297; *Abstracts of World Medicine*, 1953, 14, 110, and 1955, 18, 408), a series of 79 cases of known clinical lupus erythematosus were examined at the University and Mount Sinai Hospitals, New York. A battery of standard serological tests for syphilis (S.T.S.) was employed as well as the recently introduced immune adherence, complement-fixation, and in some cases immobilization tests employing the specific antigens of *Treponema pallidum* (T.P. tests). In 35 cases the patient's serum gave positive results with the S.T.S., while only in three were positive reactions obtained with the T.P. tests. Two of the latter patients had known syphilis, while the third result was unexplained. The authors underline the usefulness of the T.P. tests in distinguishing false positive reactors, and suggest that the T.P. complement-fixation test, because of the ease and cheapness of its performance, is the most suitable for wider use.

[The article includes a good summary of previous publications on this subject.] Allene Scott.

**Hereditary Factors in Reactive Mesenchymal Diseases ("Collagen Diseases").** III. Common Genetic Predisposition to Rheumatic Fever and Rheumatoid Arthritis. (Sulla ereditarietà delle mesenchimopatìe reattive (cosidette malattie del collagene). III. Sulla comune predisposizione genetica al reumatismo acuto primario e al reumatismo cronico primario.) NERI SERNERI, G. G., and BARTOLI, V. (1957). *Acta Genet. med. (Roma)*, 6, 25. 30 refs.

In this paper the authors examine the question whether there is a common hereditary predisposition to rheumatic fever and rheumatoid arthritis. The index cases were drawn from a consecutive series of 602 recorded at the Institute of Pathology of the University of Florence between 1940 and 1955. It was possible to examine the families of 479 of these patients, of whom 287 had had rheumatic fever and 192 rheumatoid arthritis. All these families lived in or near Florence. The examination included the first-degree relatives and, where possible, the second-degree relatives of the index cases. A similar examination was made concurrently of the families of three hundred control subjects—patients with acute or chronic infective disorders and psychoneuroses.

The authors found that among the relatives of persons with a history of rheumatic fever there was not only a higher incidence of rheumatic fever than among the relatives of the control series, but also a higher incidence of rheumatoid arthritis. For example, among the 1,445 first-degree relatives of the rheumatic fever index cases the incidence of rheumatoid arthritis was 2.6 per cent. compared with 0.4 per cent. among the 1,449 first-degree relatives of the controls. Conversely the relatives of the patients with rheumatoid arthritis not only had a higher incidence of rheumatoid arthritis, but also a higher incidence of rheumatic fever than the relatives of the controls. The incidence of rheumatic fever was 4.3 per cent. among the 1,163 first-degree relatives of the patients with rheumatoid arthritis and 2.2 per cent. for the 1,695 first-degree relatives of the controls.

The authors conclude that rheumatic fever and rheumatoid arthritis are expressions of the same genetic predisposition and suggest that a single dominant gene of variable manifestation is concerned.

[No attempt was made to match or correct for age in this survey.] C. O. Carter.

**Gastro-Intestinal Manifestations of Systemic Lupus Erythematosus.** BROWN, C. H., SHIREY, E. K., and HASERICK, J. R. (1956). *Gastroenterology*, 31, 649. 5 figs, 10 refs.

Some evidence of gastro-intestinal involvement was found in 32 out of 87 patients with proved systemic lupus erythematosus. In 25 of these the symptoms were of minor importance and responded rapidly to treatment. In the remaining seven, however, symptoms were severe; these seven cases are described in detail in the present paper.

The symptoms were shown to be due to ileus in five patients, involving the stomach, duodenum, or jejunum. In three patients with duodenal ileus the radiological appearances were similar to those seen in the superior mesenteric artery syndrome. Radiographs in one patient with acute abdominal symptoms on admission revealed a perforated ulcer on the lesser curvature of the stomach, possibly a result of steroid therapy. The authors state that the treatment of ileus in such cases as these should be conservative, although surgical drainage was carried out in one case. Factors possibly responsible for ileus were collagen deposits in the submucosa, vascular changes associated with the primary disease, and autonomic-nerve involvement.

The remaining two patients in the authors' series had both lupus erythematosus and ulcerative colitis, and the many features common to both conditions are described.

J. N. Harris-Jones.

**Examination of Skin from Patients with Collagen Disease utilizing the Combined Alcian Blue-Periodic-Acid Schiff Stain.** CAWLEY, E. P., McMANUS, J. F. A., LUPTON, C. H., and WHEELER, C. E. (1956). *J. invest. Derm.*, 27, 389. 2 figs, 13 refs.

Fibrinoid alteration of collagenous tissue, so characteristic of the so-called collagen diseases, is known to be preceded by a local increase in concentration of acid mucopolysaccharides. Structures containing acid mucopolysaccharides are selectively stained by Alcian blue, a relatively new phthalocyanine dye. A method combining Alcian blue staining with the periodic-acid-Schiff technique was used by the authors in the examination of involved skin from 28 patients with various collagen diseases, the resulting excellent colour contrast facilitating the recognition of material stained by Alcian blue (A.B.-positive material).

Although approximately constant in the several specimens from each individual collagen disease under consideration, the quantity of A.B.-positive material varied from one disease to another. Small quantities of A.B.-positive material were present throughout the upper dermis in discoid lupus erythematosus, in the near vicinity of the small vessels of the upper dermis in

morphea and generalized scleroderma, and throughout the upper dermis and in close proximity to damaged vessels in periarteritis nodosa. Small quantities of A.B.-positive material were also present throughout the upper dermis in normal skin. A.B.-positive material was remarkably abundant, by contrast, in the upper and middle dermis in dermatomyositis and disseminated lupus erythematosus.

[For details of the method of staining the original paper should be consulted.]

A. Swan.

**Pulmonary Lesions in Polyarteritis Nodosa.** SPENCER, H. (1957). *Brit. J. Tuberc.*, **51**, 123. 6 figs, 25 refs.

Five cases showing pathological evidence of pulmonary polyarteritis nodosa are reported from St. Thomas's Hospital, London. The first two cases were included in the 111 cases reviewed by Rose and Spencer (*Quart. J. Med.*, 1957, **26**, 43). Both were in middle-aged men who presented with respiratory symptoms together with evidence of extensive involvement of skin, retina, mucous membranes, and kidneys. *Post-mortem* studies revealed that, apart from widespread lesions of periarteritis nodosa in most viscera, there were particularly striking changes in the lungs and upper respiratory tract. Ulceration extended from the tongue to, and including, the larynx. There were well-defined areas of consolidation with cavitation in the lungs and, microscopically, complete loss of lung tissue. The pulmonary vasculature adjacent to these areas of cavitation showed changes typical of polyarteritis nodosa. This association of pulmonary and upper respiratory granulomata has been previously referred to as Wegener's syndrome.

The remaining three patients had pulmonary hypertension, in one as a result of emphysema and in two associated with mitral stenosis. All three patients died and in all three microscopy revealed evidence of an arteritis in the smaller pulmonary vessels. The author claims that he was able to distinguish these changes from those found commonly in pulmonary hypertension, and despite the absence of evidence of polyarteritis nodosa elsewhere, considers that these three cases are examples of pulmonary hypertensive polyarteritis.

J. N. Harris-Jones.

**Cogan's Syndrome. Report of Two Cases with Signs and Symptoms suggesting Periarteritis Nodosa.** BOYD, G. G. (1957). *A.M.A. Arch. Otolaryng.*, **65**, 24. 7 refs.

Cogan's syndrome consists of ciliary injection with granular infiltration of the cornea but no changes in the iris or fundus, together with tinnitus, severe vertigo and nystagmus, and rapid progressive deafness. There are no signs of systemic disease except eosinophilia and elevation of the erythrocyte sedimentation rate. Young males are most often affected.

The present author has seen four cases in the past 3 years in which the two conditions were associated and here reports two of them. The first patient, a man of 28, developed fever, diarrhoea, and cough, with deafness, vertigo, and tinnitus, and interstitial keratitis. All pathological tests gave negative results (except for posi-

tive reactions to *Salmonella paratyphosa B* and ragweed) and all antibiotics tried proved useless. Cortisone applied locally cured the eye condition. There was severe residual deafness and loss of cold caloric responses. In the other case there was total loss of caloric responses, severe deafness, and recurring diarrhoea with fever. There was a family history of asthma, but no personal sensitivity was found. Except for the ear symptoms improvement was obtained with cortisone and blood transfusions. In both cases at some time during the course there was lymphadenopathy and enlargement of the liver and spleen.

F. W. Watkyn-Thomas.

**Clinical Features of Polyarteritis Nodosa with Lung Involvement.** ROSE, G. A. (1957). *Brit. J. Tuberc.*, **51**, 113. 4 figs, 25 refs.

This paper from St. Mary's Hospital, London, describes the pulmonary manifestations of polyarteritis nodosa, "since these are unfamiliar and often lead to errors in diagnosis". It is based on a survey of 111 cases of polyarteritis nodosa undertaken for the Collagen Diseases and Hypersensitivity Panel of the Medical Research Council and previously reported by Rose and Spencer (*Quart. J. Med.*, 1957, **26**, 43; *Abstracts of World Medicine*, 1957, **22**, 133). The lungs were involved in one-third of these cases.

Three types of pulmonary involvement are recognized and designated respectively pneumonic, bronchitic, and asthmatic. Records of cases illustrating the three types are presented. Three cases of the pneumonic type are described. In each case extensive pulmonary disease, considered to be and treated as tuberculosis in two cases, preceded the onset of generalized symptoms, with the development of which the illness was recognized as polyarteritis nodosa. The bronchitic variety is typified by a case in a woman who presented with a productive cough and in whom radiological examination showed minimal diffuse pulmonary infiltration. An accompanying proteinuria suggested polyarteritis, and this was confirmed by muscle biopsy. Finally, two cases are described in which periodic attacks of asthma dominated the clinical picture. Despite associated symptoms such as haemoptysis, haematuria, and subcutaneous nodules, the correct diagnosis was not reached in the first case (in a woman of 40) until material removed during a lobectomy for bronchostenosis was examined. Both lungs showed cystic changes, but the disease was controlled by administration of steroids. In the second case, in a boy of 16, the diagnosis was made only at necropsy following his sudden death 17 months after the onset of illness.

There do not seem to be any specific radiological changes when the lungs are involved in polyarteritis nodosa, but the presence of diffuse miliary stippling and transient pulmonary infiltrates is regarded as suggestive, and cystic cavities of any variety may be seen. It appears that the pulmonary phase of polyarteritis nodosa may often precede generalized systemic spread of the disease, but it is not considered possible to make a diagnosis with any degree of certainty at this stage of the illness.

J. N. Harris-Jones.



**Natural History of Systemic Lupus Erythematosus: an Approach to Its Study through Chronic Biologic False Positive Reactors. Interim Report.** MOORE, J. E., SHULMAN, L. E., and SCOTT, J. T. (1957). *J. chron. Dis.*, 5, 282. 6 figs, 3 refs.

The authors of this paper from Johns Hopkins University and Hospital, Baltimore, present a re-evaluation of the natural history of systemic lupus erythematosus (S.L.E.), the absence of any specific diagnostic feature of this disease, since the L.E.-cell phenomenon does not fully serve the purpose, making such a periodic re-orientation desirable in their opinion. Their investigations started from the observation, reported by Moore and Lutz (*J. chron. Dis.*, 1955, 1, 297; *Abstracts of World Medicine*, 1955, 18, 408), that of 148 patients who gave chronic biological false positive reactions in standard lipid-antigen serological tests for syphilis and were followed up for one to 20 years, 42 per cent. eventually developed verified or probable S.L.E. or rheumatoid arthritis. The number of patients under observation has now increased to 210 and a detailed statistical analysis of the data derived from their study is in preparation. In the meantime the authors present an interim statement of their general impressions.

Consideration of the major clinical manifestations of S.L.E. leads them to conclude that the course of the disease is chronic, episodic, often relatively benign, and not necessarily fatal. No single manifestation is pathognomonic of S.L.E. episodes greatly differing in nature often succeeding each other over a period of many years separated by longer or shorter intervals, but together they may eventually prove sufficient to substantiate the diagnosis. The various clinical manifestations are collected in a table, and details of 6 illustrative cases are presented.

The authors suggest that, as was the case with syphilis, another chronic, episodic disease of many years' duration and protean manifestations, the natural history of S.L.E. will not be wholly elucidated until a satisfactory aetiological factor is discovered.

Harry Coke.

#### **Treatment of Lupus Erythematosus with Chloroquine.**

**Therapeutic Results and a Comparison of the Value of Chloroquine and Mepacrine.** CHRISTIANSEN, J. V. (1957). *Brit. J. Derm.*, 69, 157. 4 figs, 14 refs.

A comparative investigation of the effects of mepacrine and chloroquine in the treatment over a 2-year period of 137 patients with chronic lupus erythematosus is reported from the Finsen Institute, Copenhagen. Chloroquine was found to be preferable for a number of reasons. It did not cause discoloration of the skin and side-effects were fewer and less severe than with mepacrine. Therapeutic results were better with chloroquine, but with both drugs relapse was frequent. Relapse was not prevented by a low maintenance dose of chloroquine.

John T. Ingram.

**Aspiration Biopsy of the Kidney in Systemic Lupus Erythematosus.** JOSKE, R. A., and STUBBE, J. L. (1957). *Med. J. Aust.*, 1, 347. 8 figs, 48 refs.

At the Royal Melbourne Hospital aspiration biopsy of the right kidney was performed, together with a battery

of other tests, on eleven patients with systemic lupus erythematosus. The diagnosis in all cases was based on the clinical features and confirmed by the demonstration of L.E. cells in the peripheral blood. The eleven patients comprised nine females and two males, their ages ranging from 25 to 59 years. General symptoms of ill health, such as fever and loss of weight, were noted by all the patients, as were arthralgia or muscle pains. However, skin changes were present in only six. None had chronic discoid lupus erythematosus. Nine of the eleven patients were anaemic, and in five cases the Coombs test was positive. In six cases haemolysis or haemagglutinins were demonstrable in the blood. Erythrophagocytosis was demonstrated in eight cases. The serum gamma-globulin content was elevated in five of nine cases in which it was estimated. Some cardiovascular or renal involvement was present in all eleven patients, and seven of them had persistent albuminuria.

Of the eleven renal biopsy specimens, nine showed abnormal appearances, gross changes being present in five. The most frequent change was a thickening of the walls of the glomerular capillaries by an eosinophilic material which had the histochemical characters of fibrinoid. In its minimal form this process appeared as small foci throughout the glomerulus, while the glomerular capillaries remained patent. In some instances this produced the characteristic "wire-loop" appearance. In more severely affected glomeruli the process was diffuse, the lobulation of the tufts was lost, the capillary loops were diminished, and the number of nuclei in the glomerulus appeared to be increased. In its most advanced form this process resulted in obliteration of the glomerular vessels and their replacement by a whorl of avascular, acellular tissue with the staining properties of fibrinoid. The number of glomeruli contained in the biopsy specimens varied from 4 to 39, the average being 22.

The patients were followed up for periods varying from 6 months to 4 years. The "keystone of treatment" was oral cortisone (25 to 175 mg. daily). Progress in seven cases was good.

A. Swan.

**Periarteritis Nodosa.** (Über Periarteritis nodosa.) COMBERG, U. (1957). *Klin. Mbl. Augenheilk.*, 130, 850. 2 figs, 15 refs.

A case of a patient who developed a marked oedema of the left upper lid, which showed, histologically, periarteritis of the upper orbital arteries and a generalized periarteritis nodosa, is described. Diagnosis was possible only after biopsy. There is a short discussion on the aetiology, histology, and therapy. Focal allergy appears to be the most probable cause in the case described. The danger of treatment with antibiotics and possible improvement with cortisone and ACTH therapy are mentioned.—(Author's summary.)

**Cortisone Therapy of Visual Loss in Temporal Arteritis.** BENNETT, G. (1956). *Brit. J. Ophthalm.*, 40, 430. 19 refs.

In an attempt to assess the value of this treatment, six personal cases together with twenty cases cited from



the literature are analysed. In the personal cases, nine eyes were affected, and of these only three had a slight improvement in vision after treatment. Taking the total some improvement was observed in twelve out of 26 eyes affected. Reports of improvement in cases not treated by cortisone range between 3 and 20 per cent. in different series.

There appears, therefore, to be a significantly better prognosis under this therapy. J. E. M. Ayoub.

**Eye and Liver in Polyarteritis.** (Augen und Leber bei der Periarteriitis nodosa.) OTTO, H. (1957). *Z. ges. inn. Med.*, **12**, 244.

Ocular symptoms occur in polyarteritis in 10 to 23 per cent of cases. The symptoms are described, as well as the history, aetiology, and therapy of the condition. W. Leydhecker.

**Fundus Changes in Collagen Disease.** (Augenhintergrundveränderungen bei "Kollagenkrankheit".) HOTZ, G. (1957). *Ophthalmologica (Basel)*, **133**, 354.

**Collagen Disease and Ocular Manifestations. Transition between Articular and Muco-Cutaneous Syndromes.** (Collagénoses et manifestations oculaires. Transition entre les syndromes articulaires et muco-cutanés.) STUCCHI, C. (1957). *Ophthalmologica (Basel)*, **134**, 1. Bibl.

**Renal Lesions of Scleroderma.** (Les lésions rénales de la sclérodémie.) CARPENT, G. (1957). *Acta clin. belg.*, **12**, 181. 6 figs, 12 refs.

**Lupus Erythematosus.** WARD, W. H., and GUNTHER, W. W. (1957). *Aust. J. Derm.*, **3**, 159. 14 refs.

**Disseminated Lupus Erythematosus: Its Recognition and Present-Day Concepts of its Etiology and Management.** ALLGOOD, J. W. (1957). *N.C. med. J.*, **18**, 141. 2 figs, 19 refs.

**Vascular Lesions in Lupus Erythematosus.** (Lesiones vasculares en el lupus eritematoso.) BARROSO-MOGUEL, R. (1957). *Arch. Inst. Cardiol. Mex.*, **27**, 167. 6 figs, 11 refs.

**Polyarteritis Nodosa and its Treatment with ACTH or Cortisone.** [In English.] JOHNSON, S., and LEONHARDT, T. (1957). *Acta med. scand.*, **157**, 479. 3 figs, 38 refs.

**Two Cases of Chronic Disseminated Lupus Erythematosus treated successively with ACTH, Cortisone, and Chloroquine.** [In English.] REHTUÄRVI, KATRI (1957). *Acta dermat-venereol. (Stockh.)*, **37**, 242. 16 figs, 6 refs.

**Pulmonic Manifestations of Systemic Lupus Erythematosus.** CORDASCO, E. M., HASERICK, J. R., SKIRPAN, P. J., and VAN ORDSTRAND, H. S. (1957). *J. chron. Dis.*, **5**, 290. 6 figs, 14 refs.

**Disseminated Lupus Erythematosus Simulating Acute Rheumatic Fever.** MEREDITH, H. C. (1957). *Va med. Mon.*, **84**, 449. 11 refs.

**Ocular Manifestations of Collagen Disease.** MAUMENE, A. E. (1957). *Ophthalm. ib.-amer.*, **9**, 223. 2 figs, 14 refs.

**Therapy of Collagen Diseases.** LEOPOLD, I. H. (1957). *Ophthalm. ib.-amer.*, **9**, 234. 29 refs.

**Exophthalmos in Nodular Periarthritis.** [In French.] VIALLEFONT, B., BERTRAND, A., and BOULAD, —. (1956). *Rev. Oto-neuro-ophthal.*, **28**, 469.

**Differential Diagnosis of Collagen Diseases.** GUYTON, J. S. (1957). *Ophthalm. ib.-amer.*, **19**, 119. 1 fig., 10 refs.

**Diffuse Collagen Diseases.** ZIMMERMAN, L. E. (1957). *Ophthalm. ib.-amer.*, **19**, 131. 37 refs.

**Evolution of Collagen Diseases.** (Evolucion de las enfermedades del colágeno.) CONTARDO, R. (1957). *Ophthalm. ib.-amer.*, **19**, 150. 80 refs.

**Visceral Manifestations of Scleroderma (Scleroderma and Cataract).** (Manifestaciones viscerales en la esclerodermia (esclerodermia y catarata).) AGUILERA MARURI, C., and MIRAPÉIX DEL CERRO, J. (1957). *Act. dermatofiliogr. (Madr.)*, **48**, 303. 6 figs, 185 refs.

**Immunological Research in Collagen Diseases with Particular Reference to Erythematoses. I. The Presence in the Serum of Heterophil Agglutinating Antibodies.** (Ricerche immunobiologiche nelle collagenopatie con particolare riguardo all'eritematoses. I. Sulla presenza nel siero di emoanticorpi agglutinanti eterofili.) RASPONI, L. (1957). *Arch. ital. Derm.*, **28**, 451. 9 figs, 58 refs.

**Long-term Treatment of Disseminated Lupus Erythematosus with Prednisone.** (Über die Dauertherapie des Lupus erythematoses disseminatus mit Prednison.) ZIETZ, E. (1957). *Medizinische*, No. 24, 909. 54 refs.

**Lupus Erythematosus Disseminatus after Administration of Mesantoin.** LINDQVIST, T. (1957). *Acta med. scand.*, **158**, 131. 27 refs.

**Laboratory Findings in Disseminated Lupus Erythematosus.** (Hallazgos de laboratorio en el lupus eritematoso disseminado.) LOSADA L. M., CHAMORRO, G., ETCHVERRY, R., GUZMÁN, C., KATALINIC, V., DONOSO, H., and KLINGER, J. (1957). *Arch. argent. Reum.*, **20**, 1. 10 refs.

**Systemic Lupus Erythematosus.** HILL, L. C. (1957). *Brit. med. J.*, **2**, 655 and 726. 10 figs, bibl.

**Hyaluronidase in Scleroderma.** (Hyaluronidas vid scleroderma.) JOHANSSON, S., and MÖLLER, F. (1957). *Nord. Med.*, **58**, 1086. 1 fig., 17 refs.

**Dermatomyositis. A Review of Nineteen Cases in Adolescents and Children.** EVERETT, M. A., and CURTIS, A. C. (1957). *A.M.A. Arch. intern. Med.*, **100**, 70. 15 refs.

**Dermatomyositis.** SCHWARTZ, B. (1957). *Proc. roy. Soc. Med.*, **50**, 476.

**Heart Disease in Dermatomyositis.** (Die Erkrankung des Herzens bei der Dermatomyositis.) BACHER, E. (1957). *Z. ges. inn. Med.*, **12**, 769. 15 figs, 60 refs.

#### General Pathology

**Behaviour of Urinary Glycoproteins in Rheumatic and Other Diseases.** (Sul comportamento dei glicoprotidi urinari nelle malattie reumatiche e in alcune altre condizioni morbose.) BONOMO, E., and CERRETELLI, P. (1957). *Reumatismo*, **9**, 98. 3 figs, bibl.

In a study carried out at the Rheumatological Centre, University of Milan, the daily excretion of urinary acid mucopolysaccharides was determined in twelve normal subjects, seventeen patients with rheumatic diseases, and eleven others with various non-rheumatic diseases. The urinary mucoprotein excretion was also estimated in five normal and seven rheumatic subjects and the glycoprotein excretion in ten normal subjects, nine rheumatic patients, and sixteen with other diseases.

It was found that the excretion of acid mucopolysaccharides was increased in both the rheumatic patients and those with non-rheumatic diseases, the mean value being 5.5 mg. glycuronic acid per 24 hrs, compared with 3.7 mg. in normal subjects. Excretion of glycoprotein (precipitated by phosphotungstic acid) showed a similar increase, the patients having a mean of 16 mg. glucosamine hydrochloride per 24 hrs compared with 7 mg. in the controls. The differences in both these values are statistically highly significant ( $p < 0.001$ ). There was no significant difference in relation to sex, nor between patients with rheumatic disease and those with non-rheumatic disease. On the other hand there was no difference in the urinary excretion of mucoproteins between the normal subjects and the patients with and without rheumatic disease.

The authors present a graph showing the serum mucoprotein levels for each patient plotted against

urinary glycoprotein excretion. The result is a straight line, the correlation coefficient being 0.827. There is a full discussion of the literature on this subject.

David Friedberg.

**Fibrositic Nodule experimentally provoked in Ankylosing Spondylitis.** (Il nodulo fibrositico sperimentalmente provocato nella spondilite anchilosante.) GOSPODINOFF, A., and BACCARINI, V. (1957). *Rif. med.*, **71**, 8. 4 figs, 25 refs.

Experiments were carried out at the Institute of Rheumatology of the University of Rome on two patients suffering from ankylosing spondylitis and two healthy control subjects of the same age and build. In each case an ethyl chloride spray was applied for 5 seconds to a limited area of skin over the flexed elbow on two or three successive days. While the healthy subjects showed nothing but transient hyperaemia, the patients with ankylosing spondylitis each developed a small nodule under the skin at the site of stimulation which was tender on pressure and, in one case, acted as a "trigger-point" for pain radiating down the forearm. Biopsy of the subcutaneous tissue containing the nodule showed histological changes deemed to be typical of fibrositis.

L. Michaelis.

**Antistreptolysin-O Determinations in Health and in Disease.** SAINT-MARTIN, M. (1957). *Canad. med. Ass. J.*, **76**, 627. 4 figs, 26 refs.

Although the antistreptolysin-O titre is simple to estimate it has not been widely used as a routine estimation, as the results are often difficult of interpretation and it is necessary to know the prevalence of streptococcal infection and the level of antistreptolysin-O titre in the population being investigated. To provide such a base-line for these studies the author, working at the Hôtel-Dieu Hospital, Montreal, first performed this test on the sera of 1,153 presumably normal young adults aged from 15 to 40 years in the Montreal area. Of these, 648 (56.1 per cent.) showed a titre below 100 units, and 1,101 (95.5 per cent.) a titre below 250 units; thus only 4.5 per cent. had titres above 250 units.

The titres of groups of patients with various disorders were then studied. Of 46 cases of active rheumatic fever, only one was found to have a value below 100 units, while in the majority (38 cases) the value was over 250 units, the mean for the group being 665 units. In 72 patients with inactive rheumatic fever the titre was not raised so markedly, although it was still well above the normal range. Lastly, in 32 patients with rheumatoid arthritis and in 108 with miscellaneous diseases the range of titres corresponded quite well with that in the normal subjects. In further studies serial estimations of the antistreptolysin-O titre in the patients with acute rheumatic fever showed two patterns; in both the titre rose initially to a high level for about a month, but thereafter, although it sometimes fell to normal values with clinical recovery, it more often remained at a high level for many months after the disease had become inactive.

The author considers that this test is useful as an indicator of activity in rheumatic fever, and that a low antistreptolysin titre is of value diagnostically in excluding this condition.

B. E. W. Mace.

**Latex Fixation Test. I. Application to the Serologic Diagnosis of Rheumatoid Arthritis. II. Results in Rheumatoid Arthritis.** SINGER, J. M., and PLOTZ, C. M. (1956). *Amer. J. Med.*, **21**, 888. 1 fig., 15 refs.

The Rose-Waaler diagnostic test for rheumatoid arthritis depends on the ability of the serum of rheumatoid arthritic patients to agglutinate particles (sheep erythrocytes) coated with globulin (rabbit anti-sheep cell antibody). The authors, in the first of these papers from the Mount Sinai Hospital, New York, report experiments in which they showed that suspensions of polyvinyl toluene latex particles coated with commercial human gamma globulin show a similar specific agglutination reaction to arthritic sera. (Polystyrene latex can also be used.) They describe the preparation and standardization of the latex suspension, and also the results of preliminary tests of varying the methodology, including the effects of pH, of the order of addition of the reagents, the amount of gamma globulin used, the temperature, and the addition of electrolytes to the system. The method finally adopted is described [the original paper must be consulted for details]. The test result is considered positive when agglutination is observed with a serum dilution of 1 in 20 or more. In clinical trials results compared well with other established techniques. The advantages of the test are that it can be completed in a few hours, and that the reagents used are more susceptible to standardization.

In the second paper the results are reported of the use of the latex-fixation technique to test 1,380 sera, 150 of which were from confirmed cases of rheumatoid arthritis. The number of cases and percentage positivity in each clinical group were as follows: 150 cases of rheumatoid arthritis (71 per cent.); 120 of osteo- and other types of arthritis (2 per cent.); 250 of rheumatic fever and rheumatic heart disease (1.6 per cent.); eighty of diseases [unspecified] with hyperglobulinaemia (5 per cent.); twenty of lupus erythematosus (5 per cent.); 560 of non-arthritic disease (3 per cent.); and 200 normal subjects (1 per cent.). The results are compared with those of the Rose differential sheep-cell agglutination test and the Heller test in rheumatoid arthritis and various other conditions. Results for the latex fixation test were either positive or negative, whereas those for the sheep cell agglutination tests were recorded as positive, negative, or doubtful. When the tests were compared on a basis of *negative* results the findings were as follows: latex test, 28.7 per cent. in rheumatoid arthritis and 97.5 per cent. in other diseases; Rose test, 32 and 96.5 per cent.; Heller test, 26 and 95.5 per cent. Serum from some individual patients might give a positive result in one test and a negative result in another.

[This test is simpler than other specific tests for rheumatoid arthritis and promises to be as reliable.]

Allan St. J. Dixon.

**Studies of the Blood Chemistry in Collagen Disease.** (Ricerche sull'ematochimica delle malattie del collagene.) FRANCALANCIA, L. (1956). *Riv. Clin. pediat.*, **58**, 285. 13 figs, bibl.

From the Paediatric Clinic of the University of Florence the author presents the results of various biochemical investigations of the blood in three cases of dermatomyositis, two of progressive myositis ossificans, and one of scleroderma, the biochemical methods used being briefly indicated. In two cases repeat tests were carried out after 30 to 50 days. Brief case histories are given, together with the dosage of cortisone and ACTH employed in two of the cases of dermatomyositis. The results are presented in tables, and electrophoretograms are reproduced.

The total plasma protein level was usually at first within normal limits and decreased slightly under treatment. The albumin fraction, which was relatively decreased but in absolute figures was almost normal, increased considerably during treatment in two of the cases of dermatomyositis. Plasma  $\alpha_1$  globulins showed wide variation both in relative and absolute values, but were never below the mean normal value. An increase in some cases was directly proportional to the severity of the illness or its progressive character, and the value usually decreased following hormone therapy. In two cases of dermatomyositis, one of myositis ossificans, and the one of scleroderma the absolute value of  $\alpha_2$  globulin was increased, but all percentage values were in the vicinity of normal. The  $\beta$  globulin values were generally normal, except in the case of scleroderma, but the  $\gamma$  globulin levels were considerably increased in all the patients. The author favours Marmont's view that a primary noxious influence produces a change in the mesenchymal nucleoproteins, transforming them into endo-antigens, which in turn provoke antibody formation with a corresponding increase in the  $\gamma$ -globulin fraction.

The plasma lipoprotein content was normal in all cases, as also were the total lipid, cholesterol, and lipid phosphorus levels. In two cases of dermatomyositis there was, however, a marked increase in the lipid fractions during treatment, a less pronounced increase in a case treated with prednisone, and this was followed in all three cases by an increase in the  $\beta$ -globulin value. The plasma mucoprotein, total non-glucosamine polysaccharide, and glucoprotein levels were increased, especially in two cases of dermatomyositis and in the two cases of myositis ossificans, in proportion to the severity and the progress of the disease. The ratio of total polysaccharides to total proteins was increased in all cases in parallel with the polysaccharide increase but independently of the levels of the other protein fractions. The literature is extensively reviewed.

F. Hillman.

**Derivation of Certain Forms of "Fibrinoid" from Smooth Muscle.** MUIRHEAD, E. E., BOOTH, E., and MONTGOMERY, P. O'B. (1957). *A.M.A. Arch. Path.*, **63**, 213. 9 figs, 40 refs.

The authors, at the Southwestern Medical School of the University of Texas, have continued their study of the pathogenesis of the "fibrinoid" change of vascular



smooth muscle and renal glomeruli. Smooth muscle from the stomach and colon of dogs was allowed to autolyse under sterile conditions for 12 to 24 hours and then blended to form a fine suspension in saline or buffer solution. This material was injected unilaterally into the temporarily clamped renal arteries of anaesthetized dogs. The kidneys, when removed for examination 12 to 24 hours later, showed multiple infarcts, with injected material in the intertubular arteries and glomerular vessels as well as in some tubules.

The histochemical reactions of autolysed muscle were compared, in sections of these kidneys and *in vitro*, with fibrinoid in kidney sections from human cases of hypertension. Both materials were coloured red with Mallory's and Masson's trichrome stains, yellow with the Van Gieson stain, purple with the phosphotungstic-acid-haematoxylin agent, and blue with Weigert's fibrin stain. Both were sudanophil and gave positive reactions in the free potassium, free carbonyl, and protein-bound sulphhydryl procedures. Human fibrinoid gave a positive reaction to the periodic-acid-Schiff test, but autolysed muscle gave a positive reaction only *in vitro* or in frozen section, the response being negative in paraffin sections.

The similarity in staining reactions is considered to support the authors' hypothesis that fibrinoid is derived from smooth muscle. In the human cases it was sometimes seen that glomerular fibrinoid was continuous with that of the afferent arteriole, and it is suggested that fibrinoid travels along the vessel lumen to be deposited in the glomerulus.

M. C. Berenbaum.

#### Immunohistochemical Study of Lesions in Rheumatoid Arthritis. VAZQUEZ, J. J., and DIXON, F. J. (1957). *Lab. Invest.*, 6, 205. 18 figs, 10 refs.

The authors, at the University of Pittsburgh School of Medicine, Pennsylvania, have applied the fluorescent antibody technique described by Coons and others (*J. exp. Med.*, 1950, 91, 1) to the study of the characteristic lesions in three cases each of rheumatic carditis, disseminated lupus erythematosus, and rheumatoid arthritis. Fluorescein-labelled antibody to human gamma globulin was found to be strongly taken up by the altered perivascular tissues in rheumatic carditis, by the "onion-skin" perivascular splenic lesions, the walls of necrotic renal arterioles, the "wire-loop" glomerular capillaries, and the L.E.-cell inclusions in the cases of lupus, and by the necrotic centres of the subcutaneous nodules in the cases of rheumatoid arthritis. The lesions in rheumatic carditis and rheumatoid arthritis and the splenic lesions in lupus erythematosus were similarly shown to contain human serum albumin, but in much smaller amounts than gamma globulin.

No gamma globulin or serum albumin was found in normal tissues or tissues from a variety of diseases (myocardial fibrosis and infarction, renal, cardiac, and splenic arteriosclerosis, diabetic glomerulosclerosis, and renal cortical necrosis). On the other hand acutely inflamed tissues from cases of appendicitis and pyelonephritis showed a greater accumulation of serum albumin than of gamma globulin, as would be expected

if these changes were due to increased vascular permeability.

It appears, therefore, that the selective accumulation of gamma globulin in the three conditions studied is not due to the non-specific factors which would operate in a wide range of diseases, nor is it due to increased vascular permeability. A local antigen-antibody reaction is an attractive explanation, but as the authors [rightly] point out, there is no evidence so far that the gamma globulin involved is actually antibody, and this hypothesis cannot be substantiated until the antigens and antibodies involved are specifically characterized and demonstrated in the lesions.

M. C. Berenbaum.

#### Morphology of the Disturbance of Protein Metabolism in Felty's Syndrome. (Zur Morphologie der Eiweissstoffwechselstörung beim Felty-Syndrom.) MÜLLER, R. (1957). *Z. Rheumaforsch.*, 16, 129. 30 refs.

At Barmbek General Hospital, Hamburg, two fatal cases of Felty's syndrome were histologically investigated. In both cases a generalized plasmocytic hyperplasia of the lymph nodes and, to a lesser degree, of the liver was found. In addition, intra- and extra-cellular protein deposits, usually in the form of droplets, were demonstrated by various staining techniques; these droplets were present mainly in the reticulo-endothelial system where they aggregated especially around the plasma-cell infiltrations. As the author points out, similar protein deposits have been described in cases of multiple myeloma, kala-azar, malaria, and chronic sepsis, and therefore they are clearly not specific for Felty's syndrome. It is suggested that Felty's syndrome may be an atypical form of rheumatoid arthritis and not a primary metabolic disorder.

G. W. Csonka.

#### Vascular Lesions in Rheumatoid Arthritis. SOKOLOFF, L., and BUNIM, J. J. (1957). *J. chron. Dis.*, 5, 668. 6 figs, bibl.

This paper from the National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland, reports ten cases of rheumatoid arthritis exhibiting vasculitis which were observed during a period of 4 years. All these patients had subcutaneous nodules. The L.E.-cell test was negative and there was no other evidence of disseminated lupus erythematosus. In the majority the lesions were histologically indistinguishable from those of polyarteritis nodosa.

The authors discuss the possibility that steroid therapy caused the vascular lesions in these and similar cases which have been reported more frequently recently, but they conclude that "there is, at present, no substantial basis to estimate the magnitude of the postulated increased risk of their occurrence as a result of such therapy".

Oswald Savage.

#### Diffuse Interstitial Fibrosis complicating Rheumatoid Arthritis. SMITH, W. W., and ROTHERMICH, N. O. (1957). *Ohio St. med. J.*, 53, 773. 4 figs, 17 refs.



**Radioactive Iron Metabolism and Erythrocyte Survival Studies of the Mechanism of the Anaemia Associated with Rheumatoid Arthritis.** FREINREICH, E. J., ROSS, J. F., BAYLES, T. B., EMERSON, C. P., and FINCH, S. C. (1957). *J. clin. Invest.*, **36**, 1043. 11 figs, 47 refs.

**Differentiation of Certain Types of Fibrinoid and Hyalin.** MONTGOMERY, P. O'B., and MUIRHEAD, E. E. (1957). *Amer. J. Path.*, **33**, 285. 30 refs.

**Serologic Diagnosis of Rheumatoid Arthritis.** ROTHERMICH, N. O., and PHILIPS, V. K. (1957). *J. Amer. med. Ass.*, **164**, 1999. 10 refs.

**Variations in Staining Characteristics of Human Fibrin.** GITLIN, D., and CRAIG, J. M. (1957). *Amer. J. Path.*, **33**, 267. 14 figs, 19 refs.

**Experimental Arthritis. I. Morphologic Alterations in the Guinea-Pig after the Parenteral Injection of Bacterial Extracts. II. Studies with C-Labelled Polysaccharide Complexes of *Klebsiella pneumoniae* Type B.** JONES, R. S., and CARTER, Y. (1957). *A.M.A. Arch. Path.*, **63**, 472, 18 figs, 34 refs, and 484, 13 figs, 20 refs.

**Immuno-Electrophoretic Study of C-Reactive Protein.** (Étude immunoélectrophorétique de la C-réactive protéine.) BURTIN, P. (1957). *Sem. Hôp. Paris*, **33**, 2177. 3 figs, 11 refs.

**Comparison of Blood Levels obtained with Various Types of Penicillin used for the Prophylaxis of Rheumatism.** (Comparaison des taux de pénicillémie obtenus avec les diverses pénicillines utilisées pour la prophylaxie du rhumatisme.) MOZZICONACCI, P., GERBEAUX, C., DUPUY-JOIE, Y. (1957). *Sem. Hôp. Paris*, **33**, 2160. 10 figs, 45 refs.

**Technique of Serum Lipoprotein Estimation and the Lipoprotein Levels in Rheumatic Fever.** BERMES, E. W., CHRISTIAN, J. R., and McDONALD, H. J. (1957). *Tex. Rep. Biol. Med.*, **2**, 232. 9 refs.

**Comparison of the Effects of Compound 48/80, Protamine, and Turpentine Oil on Mast Cell Degranulation.** [In English.] GUSTAFSSON, B. E., and CRONBERG, S. (1957). *Acta rheum. scand.*, **3**, 189. 6 figs, 29 refs.

**Unusual Protein Component of High Molecular Weight in the Serum of Certain Patients with Rheumatoid Arthritis.** FRANKLIN, E. C., HOLMAN, H. R., MÜLLER-EBERHARD, H. J., and KUNKEL, H. G. (1957). *J. exp. Med.*, **105**, 425. 5 figs, 18 refs.

**Significance of the L.E. Cell Test.** COWLING, D. C., and THOMAS, I. D. (1957). *Med. J. Aust.*, **1**, 905. 16 refs.

**C-reactive Protein Test in Clinical Practice.** (La proteina C-reattiva nella pratica clinica.) CARCASSI, U., and PITZUS, F. (1957). *Minerva med. (Torino)*, **48**, 2399. 10 figs, 78 refs.

**Modification of the Latex-fixation Test for the Study of Rheumatoid Arthritis.** RHEINS, M. S., MCCOY, F. W., BURRELL, R. G., and BUEHLER, E. V. (1957). *J. Lab. clin. Med.*, **50**, 113. 1 fig., 2 refs.

#### ACTH, Cortisone, and Other Steroids

**Adrenal Cortical Response to Surgery. I. Effect of Anaesthesia on Plasma 17-Hydroxycorticosteroid Levels.** VIRTUE, R. W., HELMREICH, M. L., and GAINZA, E. (1957). *Surgery*, **41**, 549. 2 figs, 27 refs.

In this study, reported from the University of Colorado School of Medicine, the effect of anaesthesia on the free and glucuronic acid-(conjugated) plasma 17-hydroxycorticosteroid level and on the adrenocortical response to surgery was investigated in seventy patients aged from 5 to 81 years who were divided into four groups as follows:

- (1) 35 patients in whom, after induction with thiopentone and cyclopropane, cyclopropane alone, or nitrous oxide alone, anaesthesia was maintained on ether;
- (2) fifteen patients given thiopentone and nitrous oxide throughout;
- (3) ten patients given cyclopropane only;
- (4) ten patients receiving spinal analgesia (amethocaine).

Control blood samples were taken during the morning hours in order to equate the diurnal cycle, and after one hour of inhalation anaesthesia (after 15 to 45 minutes for spinal analgesia); a second sample of blood was taken before the start of the operation. After one hour of surgery a third sample was taken, and the plasma level of free 17-hydroxycorticosteroids estimated by the modified method of Nelson and Samuels. Conjugated 17-hydroxycorticosteroids were determined by Bongiovanni's method, with benzene-water partitioning.

The mean control level of free plasma 17-hydroxycorticosteroids for the entire group was found to be 12.8 µg. per 100 ml. plasma, a result agreeing well with other reported values. Cyclopropane, thiopentone-nitrous oxide, and spinal analgesia caused no significant rise in the 17-hydroxycorticosteroid level, only three out of the 35 patients in these groups showing an appreciable rise. Of the 35 patients maintained on ether, however, fifteen showed a significant rise in the mean value, but the effect was quite inconsistent, the other twenty showing only minor changes. Thus of the total seventy patients, eighteen showed a significant increase in the free plasma 17-hydroxycorticosteroid level, and of these fifteen had

received ether. After the operation had been in progress for one hour the plasma level of free 17-hydroxycorticosteroid rose significantly in the three groups receiving inhalation anaesthesia, but no appreciable change in level occurred in the group given spinal analgesia.

The conjugated plasma hydroxycorticosteroid level was also estimated in 24 patients, fifteen of whom received ether. Because a delay in the rise of conjugated plasma levels occurs following a rise in the free plasma level, blood samples were also taken at the end of surgery in these cases. The mean plasma values for both conjugated and free steroids were found to follow identical curves in all three groups given inhalation anaesthesia. These results show the effect of different anaesthetics on the pituitary-adrenocortical system and the authors discuss the significance of their findings. The absence of a rise in plasma hydroxycorticosteroid levels under spinal analgesia demonstrates that intact sensory pathways to the central nervous systems are necessary for the normal adrenocortical response to trauma to appear. Although some workers have reported that barbiturates cause a partial suppression of the adrenocortical response to cold and even to surgical trauma, the different premedication agents used in this study did not appear to affect the subsequent response to anaesthesia and surgery.

Discussing the mechanism by which such rises in plasma steroid levels occur the authors conclude that adrenocortical stimulation, rather than a decreased rate of steroid disappearance from the plasma, is the factor responsible.

Raymond Vale.

**Action of Cortisone and Anterior Corticotrophic Hormone on Experimental Gastritis and Gastric Ulcers.** RODRIGUEZ-OLLEROS, A., GALINDO, L. (1957). *Gastroenterology*, 32, 675. 7 figs, 46 refs.

The effect of ACTH and cortisone on the course of experimentally-induced lesions of the stomach and duodenum was studied at the University of Puerto Rico. Gastritis and erosions were induced in eighteen dogs by intramuscular injection of pancreatic juice (triple strength "panteric" powder buffered to a pH of 7.4 by potassium phosphate and disodium phosphate). Ten of the animals were also given daily injections of 30 to 40 mg. cortisone starting on the third to the fifth day; the remaining eight dogs served as controls. The erosions occurred mainly on the lesser curvature and pyloric antrum and duodenum and were usually punctiform in type. There was no difference between the control and cortisone-treated groups in the rate of healing of the gastric lesions.

In a further series of experiments in dogs "Atrophan" (Cincophen) was given in aqueous suspension by catheter in amounts of 2 g. daily for 4 days. With this procedure an ulcerative gastritis was produced. Cortisone in a dosage of 40 mg. daily was given in addition to Cincophen to a group of ten dogs who had been given the latter drug for up to eight days. The addition of cortisone did not increase the erosive gastric lesions and did not hinder the healing tendency of Cincophen-induced ulcers. The authors conclude that neither cortisone nor ACTH has any influence on experimentally-

induced gastric ulcers but that "spontaneous" human ulcers may be affected by these hormones.

I. McLean Baird.

**Urinary Porter-Silber Chromogen versus Blue Tetrazolium Chromogen as a Quantitative Index of Adrenocortical Function.** MARKS, L. J., LEFTIN, J. H., and LEONARD, M. P. (1957). *J. clin. Endocr.*, 17, 407. 2 figs, 13 refs.

The authors, working at the Boston Veterans Administration Hospital, have investigated the comparative merits of two different methods of assessing the urinary metabolites of the adrenocortical steroids. The phenylhydrazine-sulphuric acid reaction introduced by Porter and Silber (*J. biol. Chem.*, 1950, 185, 201) is specific for determining steroids with both an alpha-ketol grouping and a hydroxyl group at the C<sub>17</sub> position, but as some steroids, such as aldosterone and corticosterone, have no 17-hydroxyl groups they are not measured by this method. The method introduced by Mader and Buck (*Analyt. Chem.*, 1952, 24, 666) based on the reduction of blue tetrazolium does not depend on the presence of the 17-hydroxyl groups and can therefore be used for the estimation of steroids with only an alpha-ketol grouping at the C<sub>17</sub> position in addition to those measured by the former method.

Urine for testing was hydrolysed with  $\beta$ -glucuronidase and extracted with chloroform; chromatography was performed on "florisil" columns, which were then eluted with chloroform, 4 per cent. methanol in chloroform, and finally 25 per cent. methanol in chloroform. The 24-hour urinary excretion of Porter-Silber chromogen (PSC) and of blue tetrazolium chromogen (BTC) was determined in 42 normal adult males, in eight patients suffering from various endocrine diseases, and (after the intravenous infusion of 25 units ACTH (corticotrophin)) in five male patients with possible adrenal insufficiency. In all these groups the correlation between urinary PSC and BTC excretion as measurements of adrenocortical function was poor. The authors consider that "it is doubtful [whether] urinary BTC is as specific a measure of urinary adrenocortical metabolites as is urinary PSC".

T. D. Kellock.

**Steroid Pseudorheumatism.** ROTSTEIN, J., and GOOD, R. A. (1957). *A.M.A. Arch. intern. Med.*, 99, 545. 1 fig., 20 refs.

The authors describe five cases in which patients receiving long-term steroid therapy for rheumatoid arthritis developed symptoms of "steroid pseudorheumatism" [which is the same as the hypercortisonism described by Slocumb and others (*Ann. intern. Med.*, 1957, 46, 86; *Abstracts of World Medicine*, 1957, 22, 50)]. This syndrome manifests itself in periods of restlessness, asthenia, pains in the muscles, bones, joints, and tendons, and memory defect. The condition can be distinguished from rheumatoid arthritis by the absence of signs of articular inflammation and should be treated by gradual withdrawal of hormone therapy.

Oswald Savage.

**Risk of Tuberculosis in the Corticotherapy of Malignant Blood Diseases.** (Sur les risques de tuberculose dans la corticothérapie des hémopathies malignes.) MARCHAL, G. (1957). *Thérapie*, 12, 39.

The risk of the development of widespread tuberculosis in cases of Hodgkin's disease and acute myeloid leukaemia treated with cortisone is stressed by the author's experience of eight cases in which this occurred. A negative tuberculin reaction may give false reassurance, and the tuberculous disease is commonly unnoticed until necropsy. Isoniazid alone appears to provide ineffective antibiotic cover, and should be given in combination with streptomycin and PAS in large doses during corticotherapy in such cases. J. Robertson Sinton.

**Corticosteroids in the Aqueous Humour of the Rabbit Eye.**

GREEN, H., KROMAN, H. S., and LEOPOLD, I. H. (1957). *Amer. J. Ophthalm.*, 44, 91. 2 figs, 5 refs.

Analysis of aqueous humour showed that, in addition to the hydrocortisone previously shown to be present in the rabbit aqueous humour, there is another substance in a concentration of 1.0 µg. or less, the chromatogram of which gives a positive blue-tetrazolium test. It appears to be highly non-polar compared with the known corticosteroids, but is not identifiable with any of these.

E. S. Perkins.

**Evaluation of Adrenocortical Function with Intramuscular Injection of ACTH Gel.** DE FILIPPIS, V., and YOUNG, I. I. (1957). *New Engl. J. Med.*, 257, 1. 1 fig., 10 refs.

In this study of adrenocortical function, reported from Wayne State University College of Medicine, Detroit, the authors were concerned largely with the problems of apparent resistance to exogenous ACTH (corticotrophin). In the tests described 100 units of a high potency ACTH-gel was given intramuscularly, and the criterion of response was the rise in urinary 17-hydroxycorticosteroid excretion. Previous studies had shown that this is normally 13.8 mg. for adult males and 10 mg. for females in the 24 hours.

In 32 control subjects in the present study there was a mean rise in hydroxysteroid excretion of 19 mg. (range 5.5 to 39.4 mg.). In the steroid-induced unresponsiveness of patients who had received long-term corticoid therapy, no rise in 17-hydroxysteroid excretion occurred until the second or third day. In two out of three cases of Cushing's syndrome the rise was well above the normal. A patient with panhypopituitarism who had been main-

tained for 3 years on ACTH had a normal response to the test, but only three out of five patients with myxoedema responded normally.

The authors have encountered only five cases of apparently inadequate response in otherwise normal subjects. Two of these were found to be due to the use of ACTH of low potency, while acquired unresponsiveness to two types of ACTH was demonstrated in a third case. It is suggested that the intramuscular test is comparable in reliability to the intravenous test, provided that material of established potency is used. C. L. Cope.

**Investigation of the Action of Cortisone and Prednisone on Intravenous Glucose Tolerance.** HOLTEN, G., LUNDBAEK, K., and STAFFELDT, I. (1957). *Acta med. scand.*, 157, 257. 2 figs, 14 refs.

**Comparative Clinical Observations on the Action of Different Derivatives of Cortisone used for Local Intra- and Peri-articular Treatment.** (Osservazioni cliniche comparative sull'azione dei differenti derivati cortisonici utilizzati per trattamenti locali intra- e peri-articolari.) ROBECCHI, A., and DANEI, V. (1957). *Minerva med. (Torino)*, 48, 2203.

**Changes in Bony Tissues during Prolonged Treatment with Prednisone and ACTH.** (Modificazioni del tessuto osseo in corso di terapia protratta con prednisone e ACTH.) SCALABRINO, R., and BIANCHI, P. G. (1957). *Reumatismo*, 9, 159. 15 figs, 46 refs.

**Cardiovascular and Renal Complications of Cushing's Syndrome. Clinical and Pathological Study of Seventeen Cases.** SCHOLZ, D. A., SPRAGUE, R. G., and KERNOHAN, J. W. (1957). *New Engl. J. Med.*, 256, 833. 3 figs, 18 refs.

**Postoperative Collapse due to Adrenal Insufficiency following Cortisone Therapy.** SLANEY, G., and BROOKE, B. N. (1957). *Lancet*, 1, 1167. 2 figs, 11 refs.

**Deaths Associated with Steroid-Hormone Therapy. Analysis of 18 Cases.** ALLANBY, K. D. (1957). *Lancet*, 1, 1104. Bibl.

**Clinical Uses and Hazards of Adrenal Steroids and Their Analogues in the Management of Rheumatic Diseases.** BUNIM, J. J. (1957). *Bull. N.Y. Acad. Med.*, 33, 461. 45 refs.



## PREDNISONE IN RHEUMATOID ARTHRITIS: METABOLIC AND CLINICAL EFFECTS

BY

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The initial reports (Hench, Kendall, Slocumb, and Polley, 1949; Sprague, Power, Mason, Albert, Mathieson, Hench, Kendall, Slocumb, and Polley, 1950; Hench and others, 1950) of the antirheumatic potency of cortisone emphasized the fact that excessive doses produced not only desirable but also certain undesirable effects. At that time (1949), we expressed our hope and belief that analogues superior to cortisone would be discovered. Since then, at least seven more cortisone-like steroids have been found useful clinically; these include hydrocortisone, 9-alpha-fluorohydrocortisone (Fludrocortisone), prednisone, prednisolone, a compound whose structure is 9-alpha-fluoro, delta 1-hydrocortisone, and the two most recent additions, namely triamcinolone and 6-methyl, delta 1-hydrocortisone.

Each of these eight compounds has distinctive characteristics. Cortisone is the least costly to prepare synthetically; it is still useful in many cases and preferable in some. Hydrocortisone, apparently the major product of the normal human adrenal cortex, has proved to be superior to cortisone in local, especially intra-articular, administration. Fludrocortisone possesses a greatly enhanced anti-rheumatic effect (about ten times greater than that of cortisone, milligram for milligram); however, its effect on the retention of sodium and chloride and the excretion of potassium is even more enhanced. Thus, fludrocortisone is especially useful in the adrenal insufficiency of Addison's disease and when used in ointments for certain dermatological conditions, but the qualities that make it superior to cortisone or hydrocortisone in the management of Addison's disease interfere with its usefulness for rheumatic patients. Nevertheless, its production represented a distinct advance, because it demon-

strated that chemists could alter the steroid molecule so as to prepare synthetic compounds with even more selective effects. This paved the way for the dissociation of one effect from another, so that one or more of these effects could be enhanced relatively.

The chemical structure of prednisone (delta 1-cortisone) and prednisolone (delta 1-hydrocortisone) differs from that of cortisone and hydrocortisone, respectively, only in the possession of a double bond (hence the designation "delta") between the first and second carbon atoms in ring A of the molecule (Fig. 1, overleaf). It is this slight change that invests these synthetic cortisone-like steroids with an increased antirheumatic potency and a decreased effect on the metabolism of electrolytes when compared, milligram for milligram, with cortisone and hydrocortisone. It was hoped that a similar alteration of the 9-alpha-fluorohydrocortisone molecule might lessen the pronounced effect of that compound on electrolytes and perhaps might even enhance its great antirheumatic effect. Such did not prove to be the case, however, and the aforementioned 9-alpha-fluoro, delta 1-hydrocortisone proved to be similar in effect to 9-alpha-fluorohydrocortisone (Thorn, Renold, Morse, Goldfien, and Reddy, 1955; Bunim, 1957).

Triamcinolone has the chemical structure 16 alpha-hydroxy, 9-alpha-fluoro, delta 1-hydrocortisone. Its rheumatic potency appears to be approximately that of prednisone (Hellman, Zumoff, Schwartz, Gallagher, Berntsen, and Freyberg, 1957). Medrol, which is the afore-mentioned 6-methyl, delta 1-hydrocortisone, also is said to have about the same anti-rheumatic potency as prednisone (Glenn, Stafford, Lyster, and Bowman, 1957). Whether these two newest steroids will have additional practical therapeutic advantages remains to be determined by further clinical studies.

\* The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.



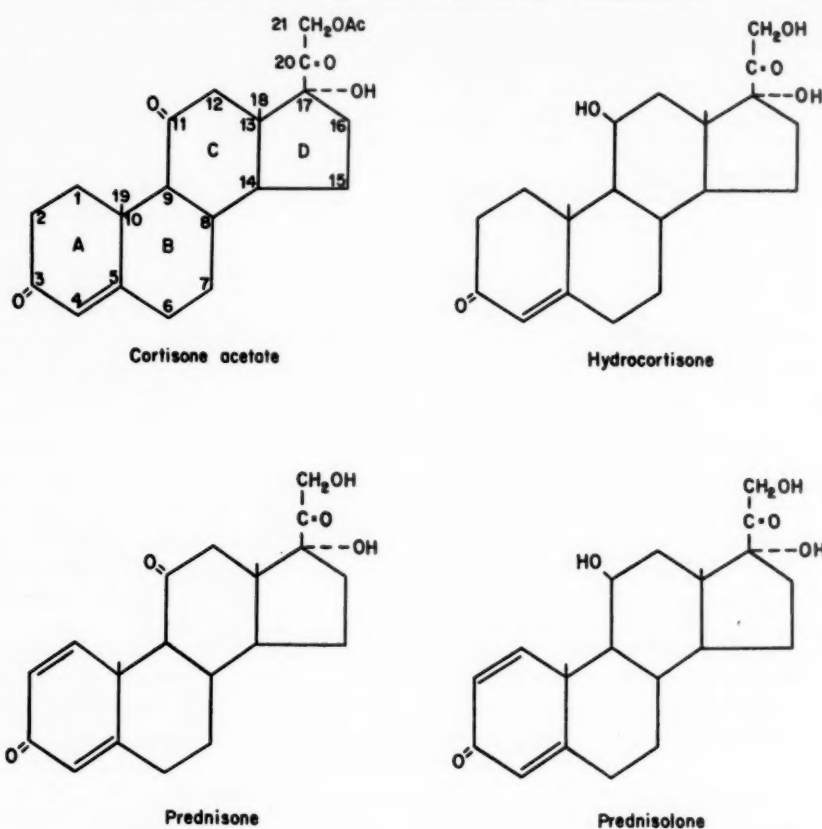


Fig. 1.—Structural formulae showing relationship between cortisone and prednisone, and between hydrocortisone and prednisolone.

### Present Study

We have studied the antirheumatic and other clinical effects of prednisone and prednisolone on many patients who had rheumatoid arthritis. In three such cases, we also made special studies concerning the metabolic effects of prednisone and in two of these three cases we compared these effects with those of cortisone or hydrocortisone.

The metabolic balances of sodium, chloride, potassium, total nitrogen, calcium, and inorganic phosphorus were studied by procedures and methods described previously (Sprague and others, 1950; Hench and others, 1950; Ward, Polley, Slocumb, Hench, Mason, Mattox, and Power, 1954; Salassa, Power, Ulrich, and Hayles, 1954). Observations were made on electrolytes, urea, uric acid, proteins, sugar, and various lipids in the blood, and on the urinary excretion of corticosteroids, 17-ketosteroids, uric acid, and creatinine; studies also were made of the erythrocyte sedimentation rate, glucose tolerance, basal metabolic rate, blood pressure,

electrocardiograms, and electroencephalograms.

### Report of Cases

**Case 1, a 51-year-old woman**, who had had severe rheumatoid arthritis for 1 year, received first a constant dose of prednisone, starting on February 27, 1955, and then hydrocortisone; after this, prednisone was given in decreasing doses. Initially, 20 mg. prednisone per day was given orally (5 mg. every 6 hrs) for 36 days, after which its use was discontinued for 12 days. Thereafter, hydrocortisone (free alcohol) was administered orally in doses of 80 mg. per day (20 mg. every 6 hrs) for 24 days. Then prednisone was again given orally as follows: 20 mg. daily (5 mg. every 6 hrs) for 6 days; 17.5 mg. daily (5 mg. at 2 a.m., 8 a.m., and 2 p.m., 2.5 mg. at 8 p.m.) for 6 days; 15 mg. daily (5 mg. at 8 a.m. and 8 p.m., 2.5 mg. at 2 a.m. and 2 p.m.) for 6 days.

**Antirheumatic Effects.**—Symptomatic relief was noted 3 hours after the first dose of prednisone, and objective improvement was noted within the first 24 hours. Both progressed rapidly so that by the 36th day of treatment the over-all improvement (loss of the patient's disability)

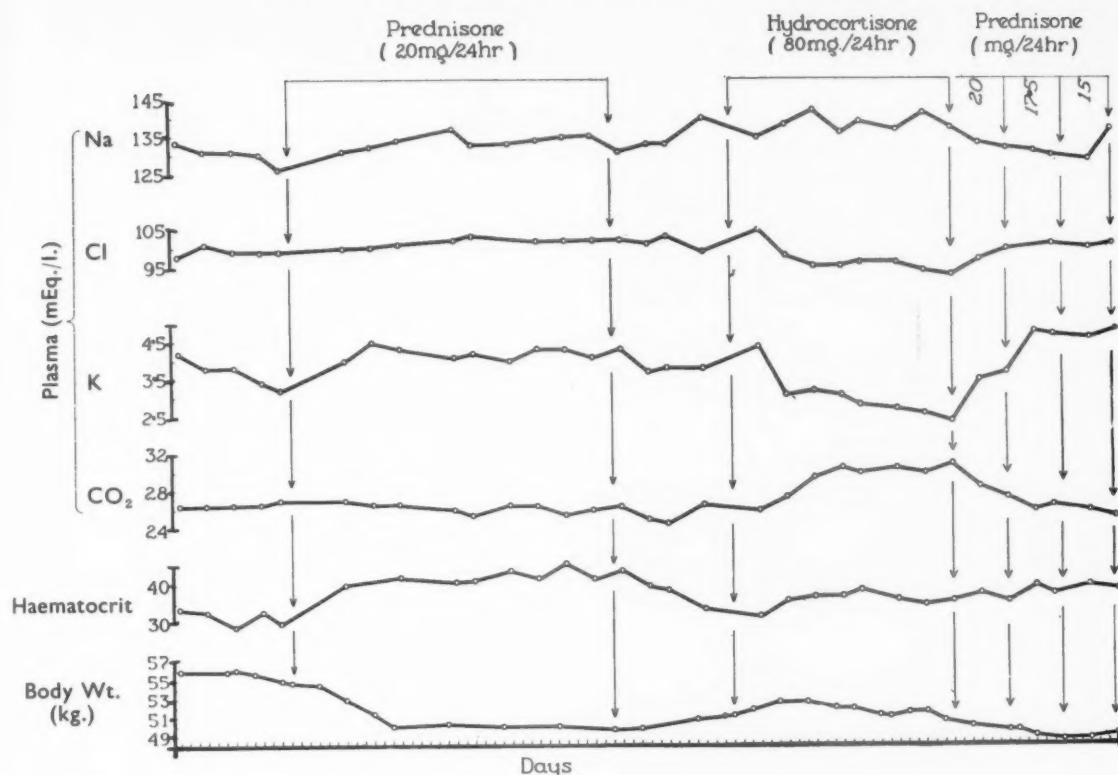


Fig. 2.—Case 1, effect of prednisone and hydrocortisone on concentration of electrolytes in plasma and on haematocrit and body weight.

was rated as 90 per cent. When administration of prednisone was stopped, rheumatoid symptoms and signs recurred rapidly. Hydrocortisone was found, as had been expected from other studies, to be only one-fourth as effective, milligram for milligram, as prednisone, 80 mg. of the former being the antirheumatic equivalent of 20 mg. of the latter. The subsequent use of prednisone in doses of 20 mg. per day maintained the same degree of symptomatic relief as 80 mg. hydrocortisone. The smaller doses of prednisone, namely 17.5 and 15 mg. daily, were proportionately less effective, as one might anticipate.

**Other Clinical Effects.**—The pitting oedema of the lower legs that was present in this patient before treatment, probably from rheumatoid inflammation, decreased notably during both courses of prednisone; the body weight decreased concomitantly (Fig. 2). On the other hand, administration of hydrocortisone led to retention of fluid, with increased oedema, presumably non-inflammatory, and body weight. Neither steroid altered the blood pressure. Both steroids produced transient mild mental stimulation (euphoria, restlessness, insomnia). Obstipation developed during the first course of prednisone. (Its occurrence in this patient and in a few others observed subsequently suggests that this rarely may be a complication of treatment with prednisone.)

**Laboratory Data.**—The laboratory data are summarized in Table I (overleaf) and Figs 2 to 5.

**Additional Sodium Chloride.**—To test this patient's tolerance for additional salt, 3 g. sodium chloride was added to the diet from the 25th to the 30th day inclusive of the first course of prednisone. This did not alter the balances or the serum levels of sodium or chloride.

**Case 2, a 54-year-old woman**, who had had rheumatoid arthritis of moderate severity for 1 year, was given 30 mg. prednisone orally per 24 hrs (7.5 mg. every 6 hrs) for 12 days, starting on July 27, 1955; then, after steroids had not been given for 12 days, she received four times as much cortisone, or 120 mg. per day orally (30 mg. every 6 hrs) for 12 days.

**Antirheumatic Effects.**—The daily dose of 30 mg. prednisone afforded 90 per cent. relief of the signs and symptoms of rheumatism, whereas the daily dose of 120 mg. cortisone afforded only 80 per cent. relief. With both steroids, the onset of relief was rapid, and disability gradually recurred after treatment was stopped.

**Other Clinical Effects.**—Both steroids produced moderate insomnia and increased hot flushes.

**Laboratory Data.**—These are summarized in Table I and in Figs 6 to 9.

TABLE I  
SUMMARY OF EFFECTS OF STEROIDS IN THREE CASES OF RHEUMATOID ARTHRITIS

Drug .. .. .			Prednisone			Hydrocortisone	Cortisone
Case No. .. .. .			1	2	3	1	2
Dose (mg. per day) .. .. .			20	30	30	80	120
Studies	Balance Studies (Excretion)	Sodium .. ..	++	+	+	⊙	0
		Chloride .. ..	++	+	+	⊙	0
		Potassium .. ..	0	0	+	++	0
		Nitrogen .. ..	+	++	++	+	0
		Calcium .. ..	—	0	—	—	0
		Phosphorus .. ..	0	+	+	0	0
	Blood Concentrations	Sodium .. ..	0	—	0	+	0
		Chloride .. ..	0	0	0	—	0
		Potassium .. ..	0	+	0	⊙	0
		Carbon dioxide .. ..	0	0	0	++	0
		Calcium .. ..	0	0	0	0	0
		Phosphorus .. ..	⊙(4.5 to 3.4 mg.)	⊙(4.3 to 3.8 mg.)	⊙(4.5 to 3.3 mg.)	⊙(4.2 to 3.0 mg.)	?(3.9 to 3.7 mg.)
		Sugar .. ..	0	0	Not done	0	0
		Lipids .. ..	++	?	+	++	?
	Urinary Steroids	17-Ketosteroids .. ..	⊙	⊙	⊙	++	++
		Corticosteroids .. ..	+	++	++	++	++
	Miscellaneous	Haematocrit .. ..	++	+	++	0	0
		Sedimentation Rate .. ..	⊙	⊙	⊙	⊙	⊙
		Haemoglobin .. ..	++ (9.7 to 11.6 g.)	0	++ (10.4 to 13.4 g.)	++ (9.3 to 10.4 g.)	0
		Glucose Tolerance .. ..	0	Diabetic-like	0	0	0
		Basal Metabolic Rate .. ..	⊙(+19 to -8)	Not done	⊙(+10 to -7)	⊙(+14 to -10)	Not done
		Electrocardiogram .. ..	0	0	0	Lowered T-wave	Not done

Key to symbols: ++ increase; + slight increase; 0 no change; — slight decrease; ⊙ decrease from period of previous medication; ? uncertain effect.

**Case 3, a 61-year-old man,** who had had severe rheumatoid arthritis for 1 year, was given prednisone in doses of 30 mg. per 24 hrs (7.5 mg. every 6 hrs) for 24 days, starting on December 25, 1954.

**Clinical Results.**—The antirheumatic effect of prednisone, first noted 7 hours after the initial dose, became pronounced within 24 hours and progressed rapidly to afford over-all reduction of at least 90 per cent. of the rheumatoid signs and symptoms; this degree of relief was sustained during administration of the steroid. Undesirable clinical effects were not present. The blood pressure was not altered. Body weight decreased by 3.5 kg. during the administration of prednisone (Fig. 10); most of this decrease was apparently caused by urinary loss of sodium, chloride, and water (Fig. 11), although some loss of nitrogen was also involved (Fig. 12). Unfortunately, further planned studies, including subsequent comparison with the effects of cortisone, had to be discontinued after 24 days of administration of

prednisone because acute severe diverticulitis developed on the 20th day. Whether the diverticulitis was related to the use of prednisone is uncertain; the signs, symptoms, and surgical pathological findings were indistinguishable from those of diverticulitis in patients who have not been treated with steroids.

**Laboratory Data.**—These are summarized in Table I and Figs 10 to 13.

**Summary of Metabolic and Clinical Data, and Comment**

**Antirheumatic Effect.**—In Case 1, prednisone was four times as potent as hydrocortisone, milligram for milligram; a daily dose of 20 mg. prednisone was the antirheumatic equivalent of a daily dose of 80 mg. hydrocortisone, both steroids producing about 90 per cent. relief. In Case 2, prednisone was about four and a half times as effective as

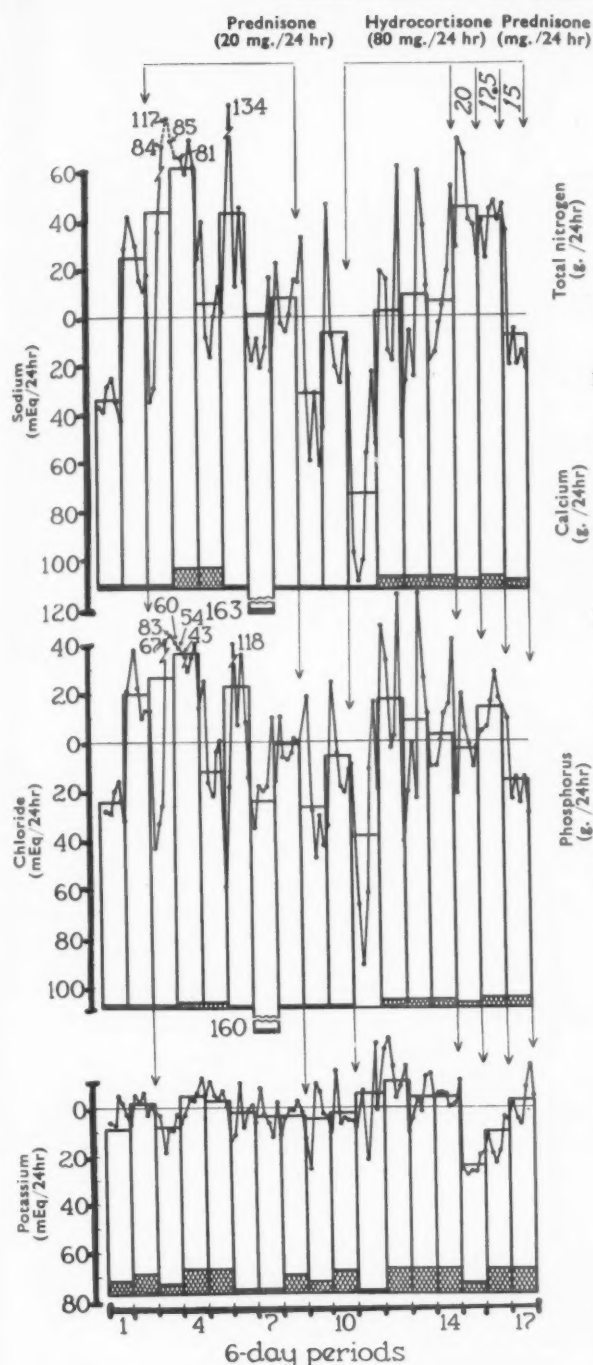


Fig. 3.—Case 1, effect of prednisone and hydrocortisone on balance of sodium, chloride, and potassium.

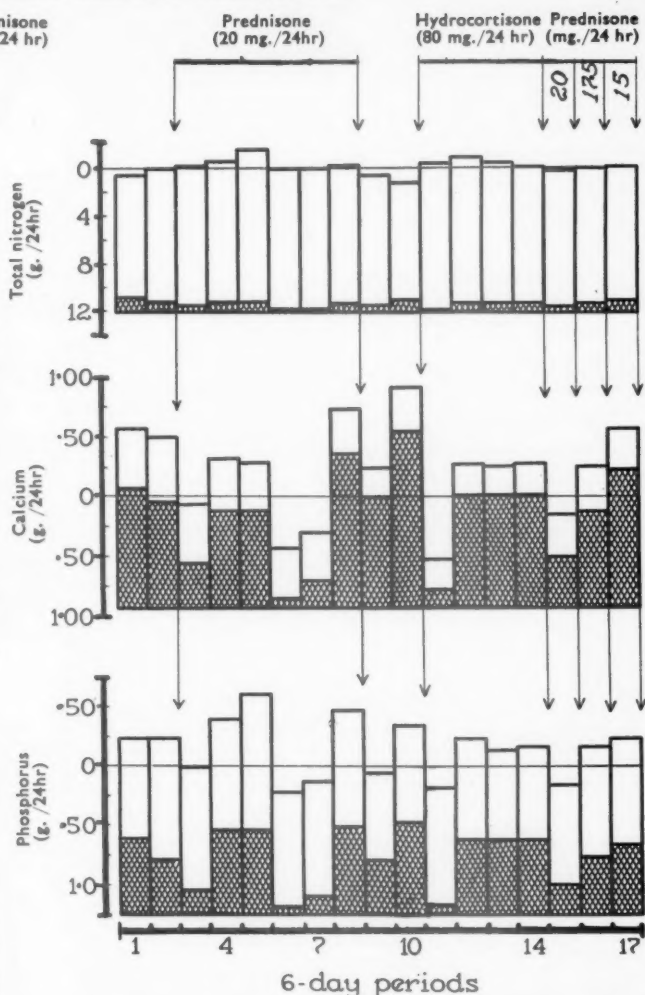


Fig. 4.—Case 1, effect of prednisone and hydrocortisone on balance of total nitrogen, calcium, and inorganic phosphorus.

cortisone; a daily dose of 30 mg. prednisone gave 90 per cent. relief, whereas a daily dose of 120 mg. cortisone gave only 80 per cent. relief. In Case 3, 30 mg. prednisone per day produced 90 per cent. relief, and comparisons with other steroids could not be made.

These results, together with those from numerous other patients whom we have studied clinically, confirm the findings of Bunim, Pechet, and Bollet (1955a) and of Boland (1955; 1956), Bunim and others (1955b), Dordick and Gluck (1955), Bunim, Black, Bollet, and Pechet (1955), Margolis, Barr, Stolzer, Eisenbeis, and Martz (1955), Spies, Stone,

In Fig. 3 and in subsequent comparable figures, daily intake is measured downward (but not blocked in) from the 0 line, and is represented by the distance from the 0 line to the bottom line of the column. The average daily excretion (faecal, hatched column; urinary, clear column) is charted upward from the bottom line. Each column represents a 6-day period. Each dot represents the daily balance calculated by subtracting from the daily intake the sum of the daily urinary excretion and one-sixth of the faecal excretion for that 6-day period. A negative balance is indicated when the top of the column or the dot is above the 0 line; a positive balance is indicated by a position below the 0 line.



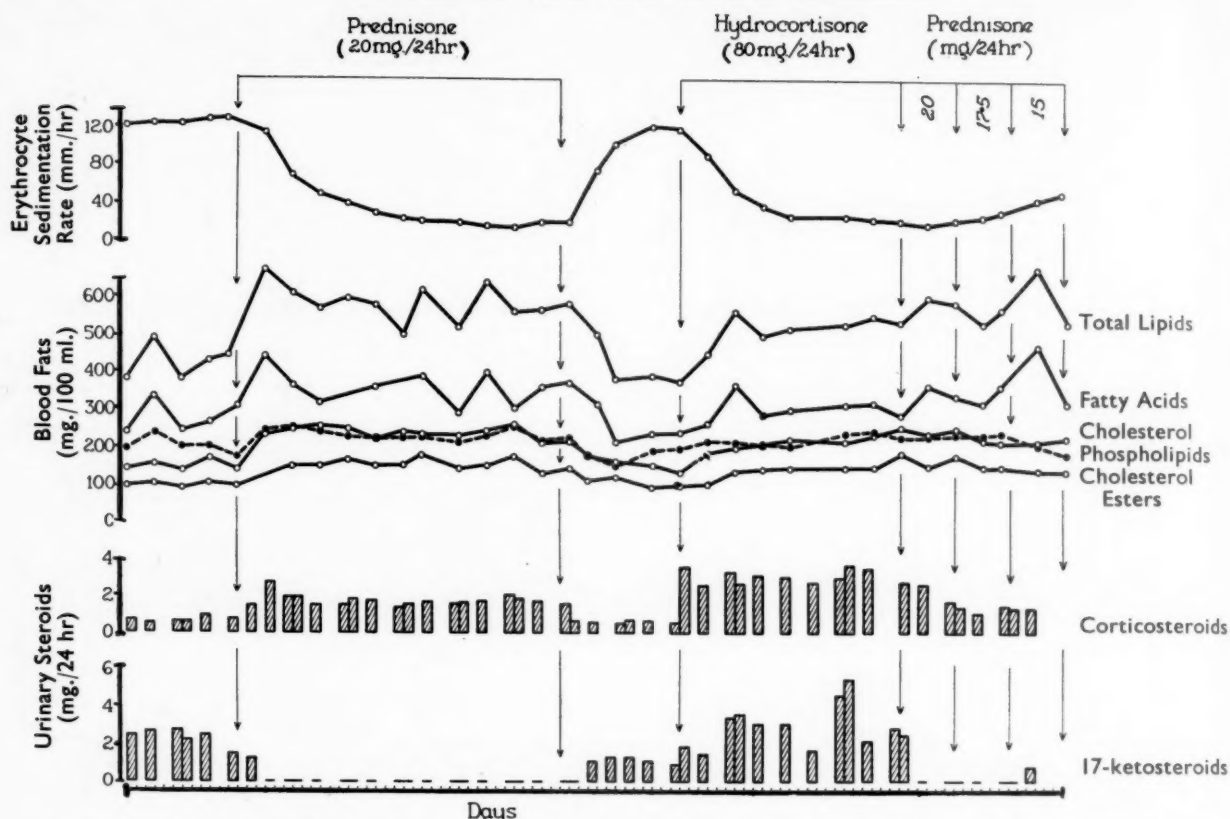


Fig. 5.—Case 1, effect of prednisone and hydrocortisone on erythrocyte sedimentation rate, concentration of blood fats, and urinary excretion of corticosteroids and 17-ketosteroids.

and Spies (1955), Villa, Ballabio, and Sala (1955), Spies, Stone, López, Tellechea, Toca, Reboredo, and Suárez (1955), Hollander (1955), Cohen, Turner, and Dunsmore (1955) that prednisone has an anti-rheumatic effect at least four or five times greater than that of cortisone or hydrocortisone, milligram for milligram. We have not observed any qualitative difference between the antirheumatic effects of prednisone or prednisolone and those of cortisone or hydrocortisone.

**Undesirable Clinical Effects.**—By undesirable side-effects, we mean effects not required or desired in a particular patient. Prednisone, given briefly to these three patients, produced only minor undesirable clinical effects in the two women. However, prednisone (or prednisolone), given in excessive doses for a sufficient length of time, can produce all the undesirable effects of excessive amounts of cortisone or hydrocortisone, as we and others have observed in other rheumatoid patients treated with these newer steroids. The undesired effects produced by prednisone were approximately the same, milligram for milligram, in the two women; such

is not always the case, of course, since different tolerances for prednisone may be found. However, men generally tolerate antirheumatic steroids, including prednisone, better than do women.

The approximately equivalent antirheumatic doses of prednisone (20 mg.) and hydrocortisone (80 mg.) in Case 1 produced about the same degree of undesired side-effects in that patient. Thus, prednisone was about four times as potent as hydrocortisone not only in antirheumatic activity but also in the production of undesired side-effects. The same general relationship obtained between prednisone and cortisone in Case 2.

It is obviously important to compare compounds in equivalent antirheumatic doses when an attempt is made to assess their relative strength with respect to other functions. However, accurate comparison of relative antirheumatic effects, far from being easily accomplished, requires considerable time, care, and a number of suitable patients. It is not difficult, early in the investigation of a new steroid, to be temporarily misled regarding its antirheumatic potency both in general and in individual cases and hence to be misled secondarily as to its relative

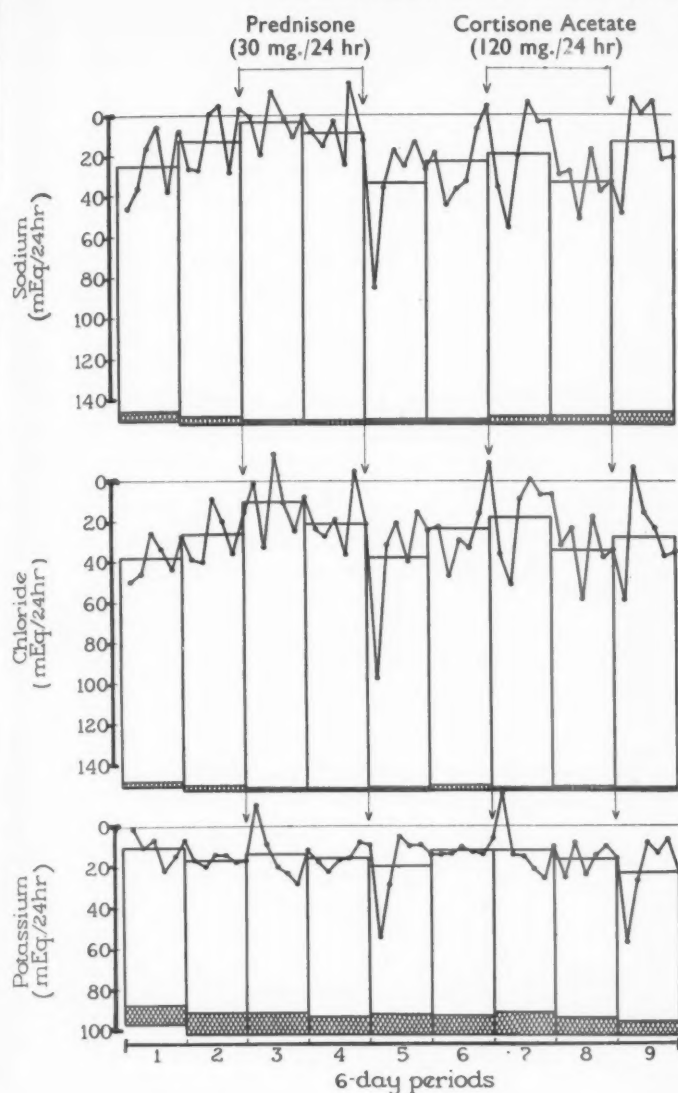


Fig. 6.—Case 2, effect of prednisone and cortisone acetate on balance of sodium, chloride, and potassium.

potential in the production of undesired side-effects. For example, when prednisone was first employed, it was thought to be about three times as potent as cortisone in antirheumatic effect. Doses based on that ratio, instead of the currently accepted ratio of about 4 : 1 or 5 : 1, led to an unexpected increase in some of the unwanted effects. Certain impressions that peptic ulcers are produced or aggravated to a greater extent by prednisone than by cortisone may have arisen, at least partially, because of the use of relatively larger doses of prednisone (Boland, 1956). On the other hand,

studies based on the initial information that triamcinolone was about twice as potent as prednisone in antirheumatic effect (Hellman and others, 1957) have already led to mistaken conclusions concerning its freedom from undesired side-effects, since more recent data suggest that the ratio is more nearly 1 : 1 (Hellman and others, 1957).

*Effect on Electrolytes.*—Prednisone caused an initial increase in excretion of sodium and chloride, whereas hydrocortisone in Case 1 and, to a lesser extent, cortisone in Case 2 led to retention of these electrolytes. Only prednisone was given in Case 3. Thus, in these short-term studies, the effects of prednisone and those of cortisone or hydrocortisone on sodium and chloride tended to operate in opposite directions. However, although there was a loss of sodium and chloride during the first 2 weeks or so of administration of prednisone, later during treatment these electrolytes tended to be approximately in balance.

Individual differences in the effect of prednisone on the sodium and chloride balances were notable, the excretion of these substances being increased most in Case 1 (20 mg. prednisone per day), less so in Case 3 (30 mg. prednisone per day), and least in Case 2 (30 mg. prednisone per day).

In Case 1, a dose of 20 mg. prednisone per day produced no effect on the potassium balance, whereas daily administration of 80 mg. hydrocortisone caused loss of potassium. Neither 30 mg. prednisone nor 120 mg. cortisone per day influenced the potassium balance in Case 2. In Case 3, a daily dose of

30 mg. prednisone caused slight loss of potassium. These data again illustrate the individual differences in response to prednisone.

Prednisone in these short-term studies caused no significant alterations in the plasma concentration of sodium, chloride, potassium, or carbon dioxide in these three cases, nor did cortisone in Case 2. In contrast, hydrocortisone in Case 1 produced hypochloreaemic, hypopotassaemic alkalosis.

These data should not be interpreted to mean that prednisone, when given in large doses for longer periods, cannot cause retention of sodium, chloride, and water or excretion of potassium. In our clinical experience, prednisone or prednisolone in

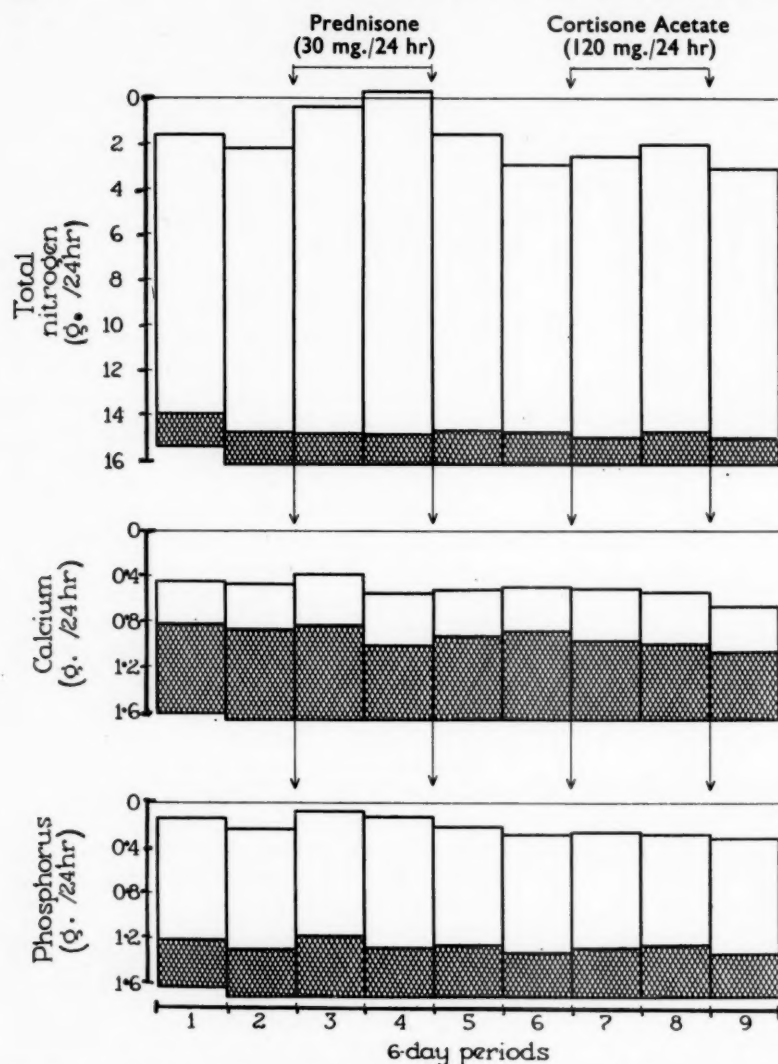


Fig. 7.—Case 2, effect of prednisone and cortisone acetate on balance of total nitrogen, calcium, and inorganic phosphorus.

doses of less than 8 to 10 mg. per day generally produces little or no oedema or hypopotassemia, even when administration is prolonged, but larger doses have produced these effects. Other observers also have reported oedema, retention of sodium, and loss of potassium during administration of prednisone.

As many others have emphasized, the effect of prednisone (Thorn and others, 1955; Dordick and Gluck, 1955; Nelson, 1955) or other corticosteroids on the excretion of sodium reflects the balance between the (usually increased) effects on glomerular filtration and on tubular reabsorption of sodium. Since the relative proportion of these two opposing effects may vary in different patients and diseases,

the total effect on the excretion of sodium also may be expected to vary.

*Effect on Nitrogenous Substances.*—Prednisone, like other antirheumatic steroids, may produce a loss of nitrogen (Thorn and others, 1955; Bunim and others, 1955a; 1955b; Bunim and others, 1955). This effect was pronounced in Cases 2 and 3 (30 mg. prednisone daily) and less so in Case 1 (20 mg. prednisone daily). Clinical experience suggests that smaller doses of prednisone, such as 5 to 8 mg. per day, often do not lead to loss of nitrogen, but may occasionally do so, particularly in postmenopausal women.

The effects of prednisone on the nitrogen balance varied notably in these three patients and, rather surprisingly, were most pronounced in the man (Case 3). It is also noteworthy that, in Case 2, although the steroids were given in comparable antirheumatic doses, prednisone produced a moderate loss of nitrogen, whereas cortisone caused little loss, if any. However, the effects on nitrogen balance of equivalent antirheumatic doses of prednisone and hydrocortisone were approximately the same in Case 1. These data pointedly indicate the individual variation in response that may be expected from patient to patient.

Prednisone, as well as other antirheumatic steroids, can produce an increase in serum albumin and a decrease in serum globulin. Such changes occurred in Cases 1 and 3 without any change in the total serum protein.

Prednisone, cortisone, and hydrocortisone did not alter significantly the amount of uric acid in the serum and urine of these three patients, although larger doses might be expected to increase the urinary excretion of uric acid. None of these steroids affected the concentration of urea in the blood or the urinary excretion of creatinine.

*Effect on Calcium and Phosphorus.*—Active rheumatoid arthritis may produce osteoporosis and a slightly negative calcium balance; these changes

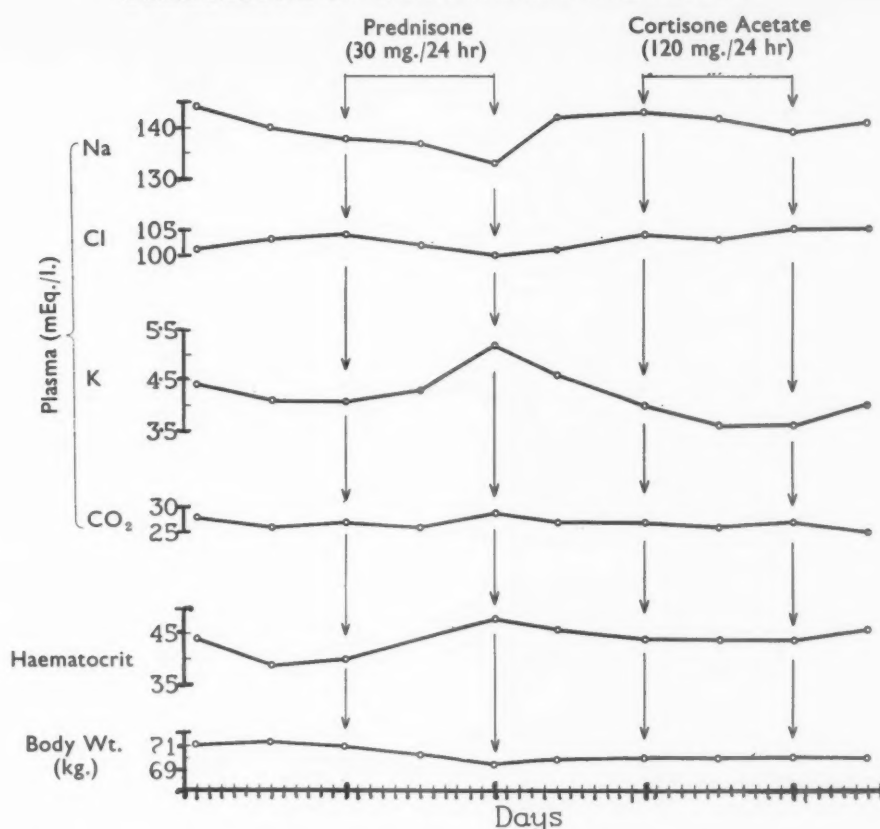


Fig. 8.—Case 2, effect of prednisone and cortisone acetate on concentration of electrolytes in plasma and on haematocrit and body weight.

apparently result not from a primary disturbance of calcium metabolism but rather from a disturbance in protein metabolism and interference with formation of bone matrix (Clark, Bauer, Appleton, and Manning, 1956). Such was apparently so in Cases 1 and 3. The administration of prednisone in these two cases, and of hydrocortisone in Case 1, led to slightly less negative calcium balances, suggesting the possibility of a decrease in the rate of production of osteoporosis, although other metabolic processes, as yet poorly understood, may be responsible for this effect. The calcium balance, initially positive in Case 2, was not appreciably affected by prednisone or cortisone. The concentration of calcium in the serum was not altered by any of the steroids administered to these three patients.

The slight increase in excretion of phosphorus in Cases 2 and 3 was approximately the amount that would be expected in a theoretic phosphorus balance calculated from the nitrogen and calcium balances; thus, it would appear that any tendency for phosphorus to be retained along with calcium was exceeded by loss of phosphorus along with nitrogen

from protoplasm. Concentration of inorganic phosphorus in the serum decreased somewhat in all cases during administration of the various steroids.

**Effect on Carbohydrate Metabolism.**—Although values for blood sugar in the fasting condition were not affected in these three cases, results of the glucose tolerance test became slightly positive (a diabetic-like curve) in Case 2 on a daily dose of 30 mg. prednisone but not on a daily dose of 120 mg. cortisone. We have observed that prednisone may aggravate the diabetic status, usually only slightly or moderately, in rheumatoid patients who also have diabetes mellitus as others have also noted (Dordick and Gluck, 1955; Bunim and others, 1955; Villa and others, 1955; Cohen and others, 1955).

**Effect on Blood Fats.**—Administration of prednisone and cortisone or hydrocortisone may increase the blood fats (Bunim and others, 1955a; Dordick and Gluck, 1955; Bunim and others, 1955; Villa and others, 1955; Wang, Bossak, and Adlersberg, 1955; Adlersberg, Schaefer, and Drachman, 1950). This was most apparent in Case 1, in which the effects of equivalent antirheumatic doses of



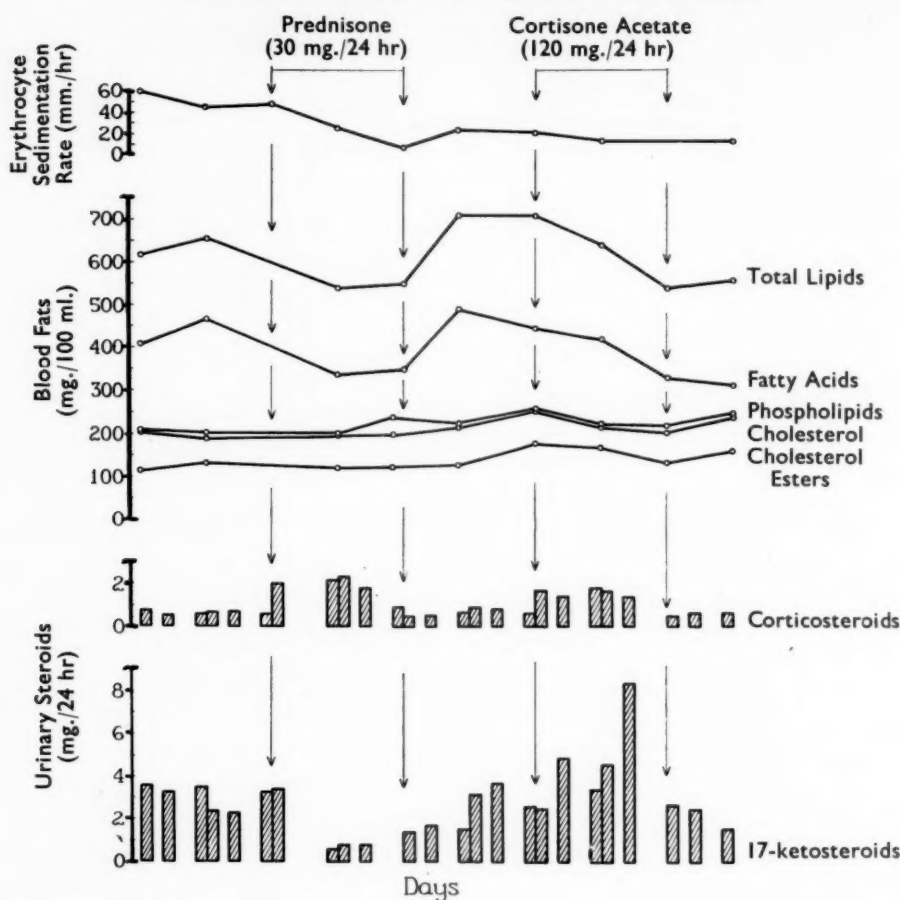


Fig. 9.—Case 2, effect of prednisone and cortisone acetate on erythrocyte sedimentation rate concentration of blood fats, and urinary excretion of corticosteroids and 17-ketosteroids.

prednisone and hydrocortisone produced rather similar increases in blood fats. Again, individual variation was evident, since the effects were less notable in Cases 2 and 3, even though the doses of steroids were greater.

**Effect on Circulating Blood Cells.**—Prednisone produced changes in circulating blood cells similar to those produced by cortisone or hydrocortisone, namely a tendency to an increase in haemoglobin and neutrophilic polymorphonuclear cells and a decrease in lymphocytes, eosinophils, and basophils (Thorn and others, 1955; Bunim and others, 1955a; Dordick and Gluck, 1955; Villa and others, 1955; Hollander, 1955; Cohen and others, 1955).

**Effect on Urinary Excretion of Steroids.**—Prednisone decreased the urinary excretion of 17-ketosteroids and increased the urinary excretion of formaldehydogenic corticosteroids in these three patients. This decrease in 17-ketosteroids, also noted by others (Bunim and others, 1955a; Bunim

and others, 1955; Villa and others, 1955), suggests inhibition of endogenous pituitary-adrenocortical function by prednisone, as by the other antirheumatic steroids at present available. These data and those on other rheumatoid patients indicate that prednisone given in doses about one-fourth or one-fifth those of cortisone produces equivalent inhibition of pituitary-adrenocortical function, as well as equivalent antirheumatic effects. The increase in corticosteroids in the urine was not necessarily of the same degree in different patients or in the same patient from day to day. Another individual difference was seen in the fact that urinary corticosteroids were increased more in Case 2 by 30 mg. prednisone than by 120 mg. cortisone, whereas urinary corticosteroids in Case 1 were increased more by 80 mg. hydrocortisone than by 20 mg. prednisone.

**Effect on Basal Metabolic Rate, Electrocardiogram, and Electro-encephalogram.**—Prednisone caus-

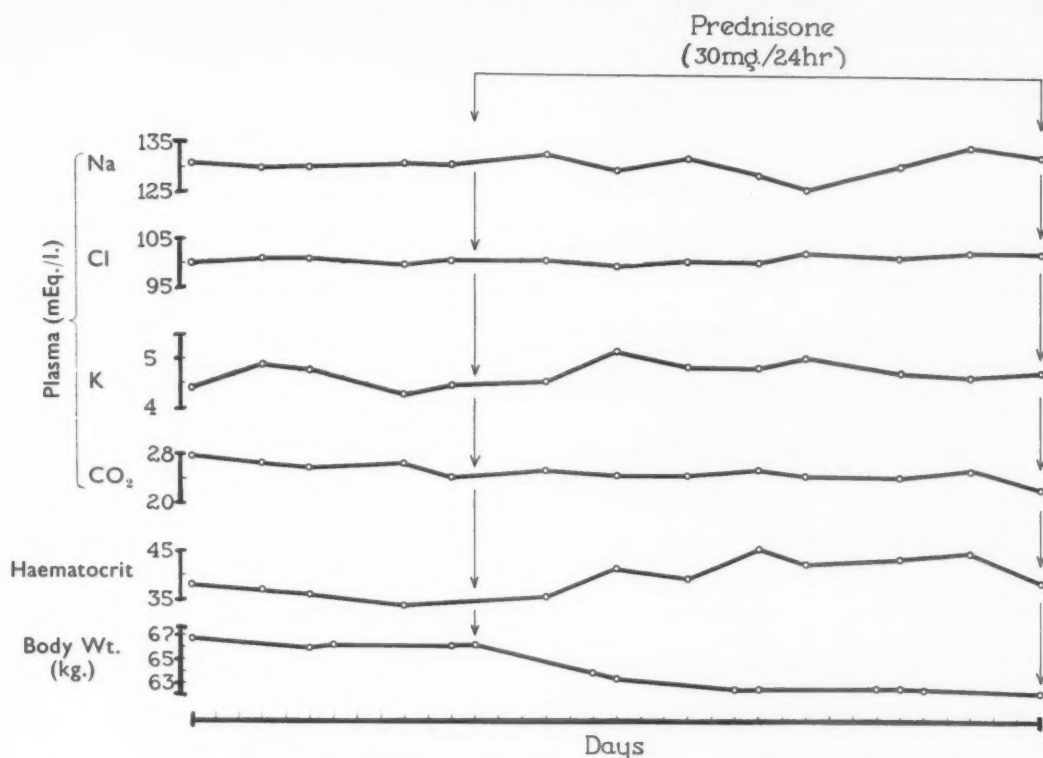


Fig. 10.—Case 3, effect of prednisone on concentration of plasma electrolytes and on haematocrit and body weight.

ed a decrease of no apparent significance in the basal metabolic rate, as has been noted previously during use of cortisone or hydrocortisone (Sprague and others, 1950). Such decreases have been attributed to improvement in the rheumatoid arthritis as well as to more direct but less certainly defined effects on the metabolism of the thyroid gland and its hormone (Sprague and others, 1950; Thorn, Jenkins, Laidlaw, Goetz, Dingman, Arons, Streeten, and McCracken, 1954). Prednisone did not alter the electroencephalograms or the electrocardiograms, although hydrocortisone-induced hypopotassemia led to lowered T-waves in the electrocardiogram of one patient (Case 1).

#### Comments on Clinical Use of Prednisone and Prednisolone in Rheumatic Diseases, especially Rheumatoid Arthritis

Prednisone and prednisolone, like their predecessors, cortisone and hydrocortisone, are useful antirheumatic steroids. Their lessened effect on electrolytes is especially advantageous for patients who have a tendency to retain fluid or lose potassium, or for patients who require comparatively

large doses of an antirheumatic steroid, as in acute rheumatic fever or a severe flare of systemic lupus erythematosus. However, previously available steroids such as cortisone or hydrocortisone, as we used them (Ward, Polley, Slocumb, and Hench, 1953; Hench and Ward, 1954), seldom caused serious or uncontrollable disorders in electrolytes when the doses employed for prolonged treatment of uncomplicated rheumatoid arthritis were small enough to avoid other manifestations of hypercortisonism. In respect to the production by overdosage of other undesirable effects, such as obesity, supraclavicular fat pads, hypertrichosis, acne, psychic changes, osteoporosis, peptic ulcers, striae, purpura, and hypertension, prednisone and prednisolone are generally similar to cortisone or hydrocortisone in equivalent antirheumatic doses.

The use of prednisone or prednisolone in rheumatoid arthritis requires the same general precautions as the use of cortisone or hydrocortisone (Ward and others, 1953; Hench and Ward, 1954):

(1) A clear-cut indication must exist for their use, such as active rheumatoid arthritis not satisfactorily managed by physical therapy, salicylates and rest, or, in some cases, gold.

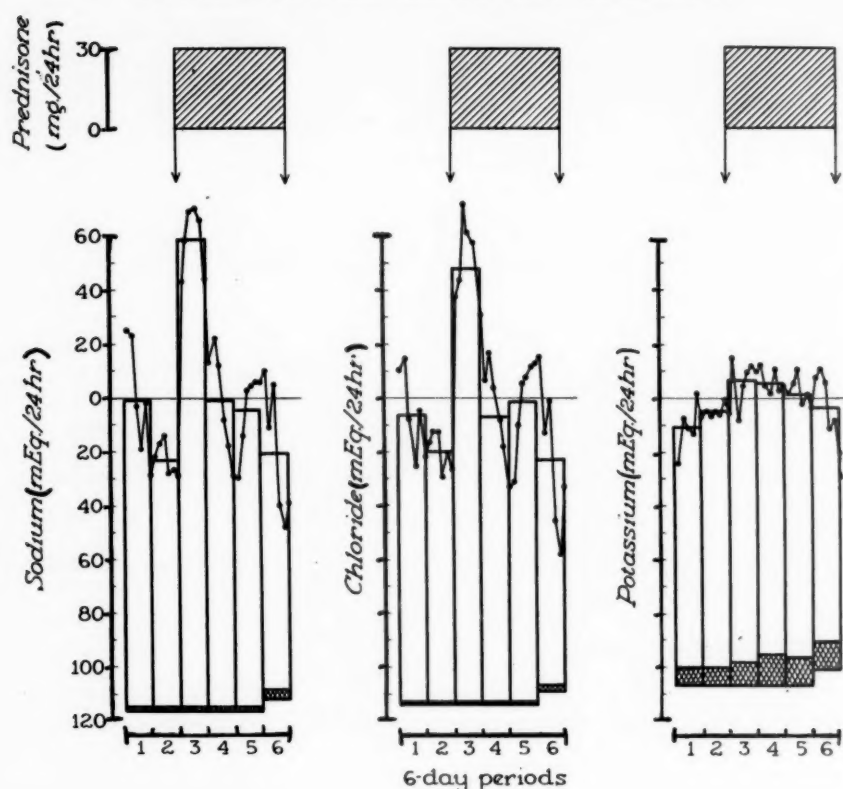


Fig. 11.—Case 3, effect of prednisone on balance of sodium, chloride, and potassium.

(2) Before treatment, a careful medical examination should be performed, with particular emphasis on those special features of the history, physical examination, and laboratory studies that are capable of uncovering potential conditions which might contraindicate or complicate the use of steroidal therapy.

(3) The physician should recheck the patient at frequent intervals to evaluate his progress, to regulate dosage, and to note and care for any side-effects or impending complications (Hench and Ward, 1954). In lieu of oedema as an early manifestation of hypercortisonism, the physician must watch for other signs, such as mental stimulation, increased appetite, gain in weight beyond the patient's predisease weight, slight facial hypertrichosis, minor degrees of facial rounding and supraclavicular fat pads, increase in blood pressure, and menstrual irregularities or increased menopausal symptoms.

(4) Doses should be measured individually to provide an optimal antirheumatic effect without hypercortisonism. Not only the total 24-hr dose, but also each 6-hr or 8-hr dose should be adjusted to fit each particular case. Individual requirements and tolerance for prednisone or prednisolone, like those for other antirheumatic steroids, may vary considerably. Hypercortisonism will develop in many instances during prolonged administration of

prednisone or prednisolone if the doses shown in Table II are exceeded or, in some cases, even maintained.

TABLE II  
UPPER LIMIT OF MAINTENANCE DOSES OF  
STERIODS IN RHEUMATOID ARTHRITIS

Patients	Dose (mg.)*		
	Cortisone	Hydrocortisone	Prednisone or Prednisolone
Postmenopausal Women	30	25	6
Premenopausal Women	40	35	8
Men	50	45	10

\* In most cases, the doses should be slightly less than these.

It is generally better to start with doses within a reasonable range for prolonged administration than to give large initial doses. If hypercortisonism develops during treatment, the dose should be decreased gradually to permit disappearance of the manifestations of overdosage. Several days or even a week or more should be allowed between decreases in dosage to permit the patient to adjust himself to the new dosage; reductions usually should be small, not exceeding 0.5 to 1 mg. at

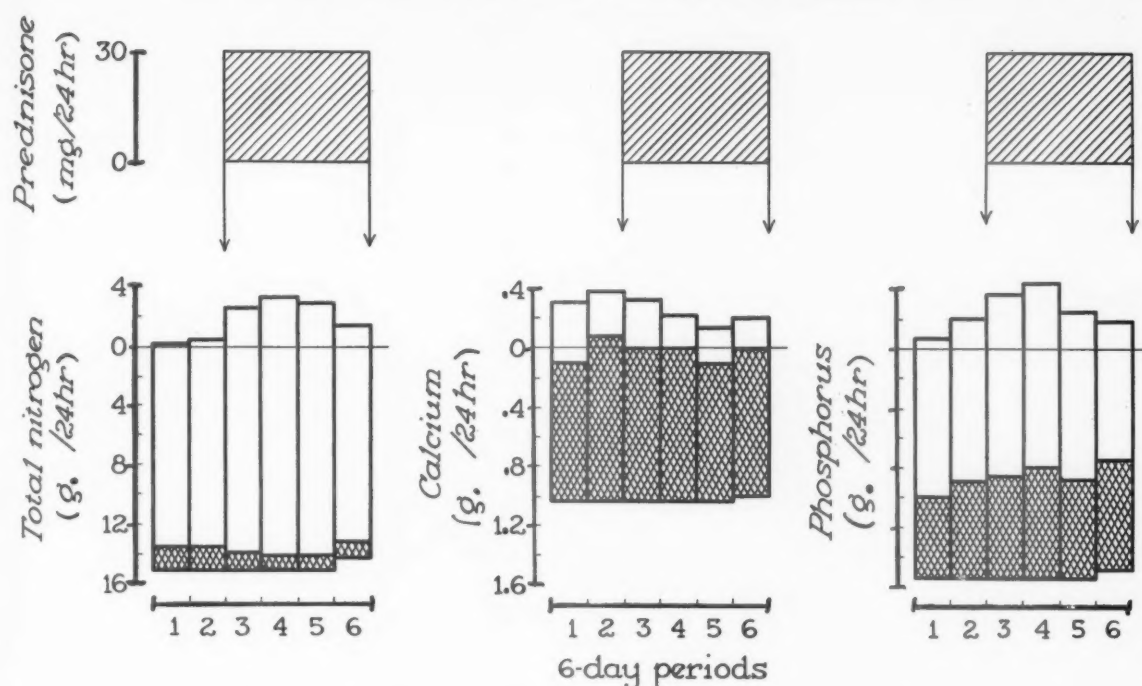


Fig. 12.—Case 3, effect of prednisone on balance of total nitrogen, calcium, and inorganic phosphorus.

a time. The daily dose of the steroid must be divided into at least three, and sometimes four, parts, administered regularly every 6 or 8 hrs. Some variation in the size of these individual doses during the 24-hr period is often necessary to meet the particular needs of the patient (Hench and Ward, 1954). Dosage schedules should be sufficiently flexible to permit the intelligent, co-operative patient to select, within certain prescribed limits, a slightly larger dose for days when symptoms are worse and a slightly smaller dose for "good" days. Eventual discontinuation of steroidal therapy by gradual reduction of dose is desirable when possible.

(5) In the event of unusual stress, such as a major operation, serious infection, or severe trauma, supplementary amounts of cortisone or hydrocortisone should be administered and other special precautions should be taken to avoid the consequences of pituitary-adrenocortical insufficiency (Hench and Ward, 1954).

(6) Treatment of rheumatoid arthritis with prednisone or prednisolone (as well as with cortisone or hydrocortisone) should be supplemented by other appropriate measures, such as physical therapy, salicylates, and rest. Salicylates, useful not only for their analgesia but also for their apparent mild anti-inflammatory effect, should be given to the limits of optimal relief and comfortable tolerance, and their administration should be continued at such limits even when rheumatoid symptoms are improving and the dose of the antirheumatic steroid is being reduced.

### Summary

Prednisone (or prednisolone) given to patients who have rheumatoid arthritis produces similar effects to those produced by cortisone or hydrocortisone with respect to antirheumatic action, influences on the metabolism of nitrogen, carbohydrate, and fat, suppression of pituitary-adrenocortical function, and influences on blood cells and the basal metabolic rate.

However, two important differences are noteworthy:

(1) Prednisone is at least four or five times as potent as cortisone or hydrocortisone, milligram for milligram, both in antirheumatic effects and in most of the metabolic effects studied to date, except those relating to electrolytes;

(2) Prednisone has relatively less effect on the metabolism of electrolytes and hence produces less retention of sodium, chloride, and water, and less excretion of potassium, in comparison with cortisone or hydrocortisone in equivalent antirheumatic doses.

The clinical use of prednisone or prednisolone must be attended by the precautions previously established for the optimal use of cortisone or hydrocortisone, namely careful selection of patients, proper medical supervision during treatment,



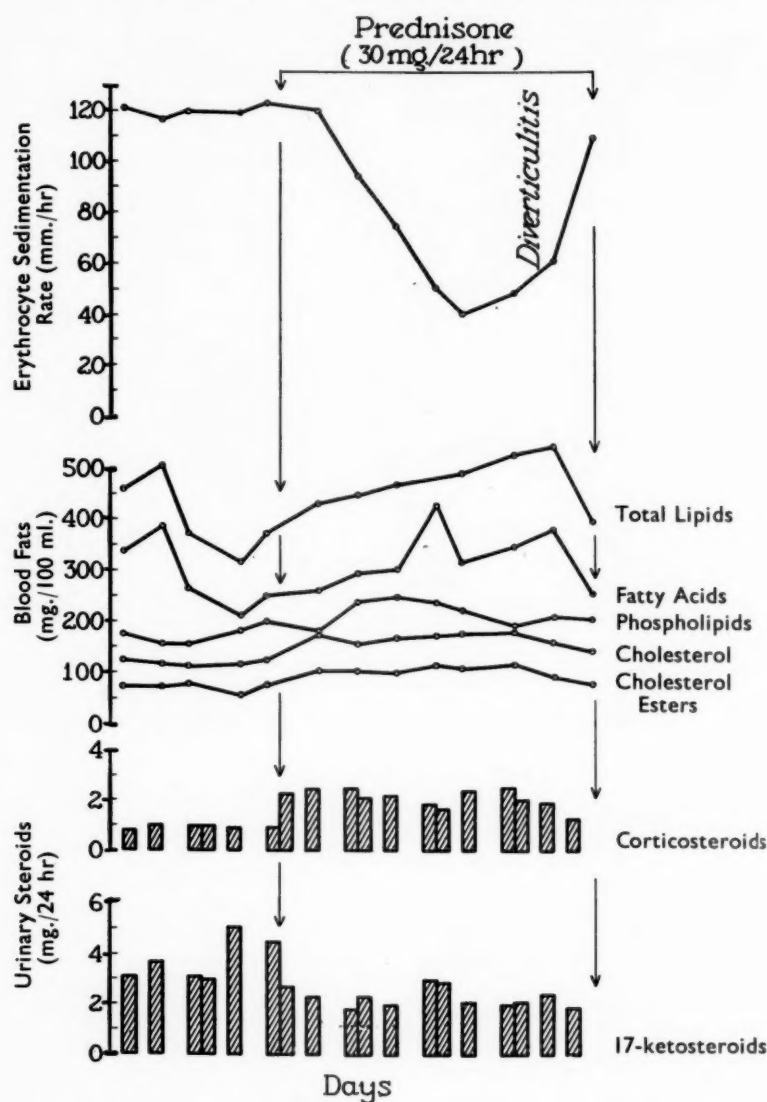


Fig. 13.—Case 3, effect of prednisone on erythrocyte sedimentation rate, concentration of blood fats, and urinary excretion of corticosteroids and 17-ketosteroids.

individual dosage schedules to provide optimal antirheumatic effects without hypercortisonism, special precautions at times of increased stress, and appropriate supportive and supplementary therapy.

The synthesis of these new cortisone-like steroids, prednisone and prednisolone, like that of fludrocortisone, is of great importance in providing further evidence that the basic structure of cortisone can usefully be altered.

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# La prednisone dans l'arthrite rhumatoïdale: effets cliniques et métaboliques

## RÉSUMÉ

La prednisone (ou la prednisolone) administrée aux malades atteints d'arthrite rhumatoïdale a la même action que la cortisone ou l'hydrocortisone en ce qui concerne l'effet antirhumatisme, le métabolisme azoté, hydrocarboné et lipide, la suppression de la fonction surrénocortico-pituitaire et l'influence sur les globules sanguins et le métabolisme basal.

On note, cependant, deux différences importantes:

(1) La prednisone, à poids égal, est au moins quatre ou cinq fois plus puissante que la cortisone ou la hydrocortisone en ce qui concerne son action antirhumatisme et ses effets métaboliques étudiés, à l'exception de ceux sur les électrolytes.

(2) L'effet de la prednisone est relativement moindre sur le métabolisme des électrolytes; la rétention sodique, chlorurée et aqueuse, ainsi que l'excrétion potassique sont, par conséquent, moins prononcées qu'avec la cortisone ou l'hydrocortisone à doses antirhumatisme égales.

En clinique, la prednisone ou la prednisolone exigent les mêmes mesures de précaution que la cortisone ou l'hydrocortisone, c'est-à-dire une sélection soignée des malades, surveillance médicale étroite pendant le traitement, administration adaptée aux besoins du malade individuel, de manière à obtenir un effet antirhumatisme optimum sans hypercortisonisme, soins spéciaux en temps de tension augmentée et thérapie supplémentaire et de soutien appropriée.

La synthèse des stéroïdes genre cortisone, tels que la prednisone, la prednisolone et la fluorocortisone est importante car elle montre que la structure essentielle de la cortisone peut être modifiée avantageusement.

# La prednisone en la artritis reumatoide: efectos clínicos y metabólicos

## SUMARIO

La prednisone (o la prednisolona), administrada a enfermos con artritis reumatoide, se parece a la cortisona o la hidrocortisona en su efecto antirreumático, sobre el metabolismo nitrogenado, hidrocarbonado y lípido, sobre la supresión de la función suprarreno-córtico-pituitaria y en su influencia sobre los glóbulos sanguíneos y el metabolismo basal.

Se notan, sin embargo, dos diferencias importantes:

(1) La prednisone, a peso igual, es al menos cuatro o cinco veces más poderosa que la cortisona o la hidrocortisona en su acción antirreumática, así como en sus efectos metabólicos estudiados, con excepción de los efectos sobre los electrolitos.

(2) El efecto de la prednisone es relativamente menor sobre el metabolismo de los electrolitos; la retención sódica, clorurada y acuosa, así como la excreción potásica son menores que con la cortisona o hidrocortisona en dosis antirreumáticas iguales.

En clínica, la prednisone o la prednisolona exigen la misma cautela que la cortisona o la hidrocortisona, quiere decir, una selección cuidadosa de enfermos, vigilancia médica apropiada del tratamiento, administración adaptada a las necesidades individuales para obtener un efecto antirreumático óptimo sin hiper-cortisonismo, cuidados especiales en tiempo de tensión aumentada y terapia suplemental y de soporte apropiada.

La síntesis de esteroides del tipo de cortisona, como la prednisone, la prednisolona y la fluorocortisona es importante, por demostrar que la estructura esencial de la cortisona se puede modificar provechosamente.

## GENETIC STUDIES ON RHEUMATOID ARTHRITIS

BY

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Though there has been much speculation on the causes of rheumatoid arthritis, the fundamental mechanism remains obscure. There have, however, been indications that a hereditary factor is present (Falls, 1953). Kroner reported four generations of rheumatoid arthritis in one family, the disease being apparently transmitted by the females. Papp and Tepperberg (1937), in another family, recorded eleven persons with rheumatoid arthritis in four generations. Kaufmann and Scheerer (1928) found a greater concordance in monozygotic than in dizygotic twins. Short, Abrams, and Sartwell (1952) recorded a prevalence of 12 per cent. in rheumatoid arthritic families, but of only 5 per cent. in controls and in the series of Stecher, Solomon, and Wolpaw (1952), the prevalence was 5 and 0.1 per cent. in rheumatoid families and controls respectively. In the Empire Rheumatism Council's Report on aetiological factors in rheumatoid arthritis (Lewis-Faning, 1950), 7 per cent. of the fathers of patients as compared with 3 per cent. of the fathers of controls and 15 per cent. of the mothers of patients as opposed to 9 per cent. of the mothers of controls had arthritis. For siblings the figures were 4 per cent. against 2 per cent. Similar figures were obtained by Barter (1952) in a comparison of the family histories of 100 rheumatoids with 100 controls who were non-rheumatic hospital patients. Miall (1955) noted a prevalence of 3 per cent. in the parents and siblings of 59 males with rheumatoid arthritis taken from a population sample in South Wales, but only 0.6 per cent. in the parents and siblings of controls of the same age, taken at random from the local population. De Blécourt (1957) examined over 2,000 relatives of persons with rheumatoid arthritis and a similar number of controls; prevalences ranged from 0.6 per cent. in male cousins to 10 per cent. in mothers of persons with rheumatoid arthritis (average 2.3 per cent.).

In the controls the prevalence of rheumatoid arthritis varied from 0.2 per cent. in male cousins to 3 per cent. in mothers (average 0.8 per cent.).

These figures, though they give clear evidence of a hereditary influence, do not indicate that this is very important, since the prevalence in other members of the family is not much greater than in the controls. Several factors may, however, have tended to obscure the genetic effect in these studies. Rheumatoid arthritis as diagnosed in the probands may not have been homogeneous, but may have included a number of diseases with similar clinical features, only one of which had a genetic basis. Furthermore, the disease in the hereditary form may be of low expressivity so that in its milder forms it is not recognized as such by the relatives of the rheumatoids, or it may indeed be completely symptomless. With a view to obtaining more definite information on these points a more detailed survey has been made of the families of persons found to have rheumatoid arthritis in the survey of rheumatic diseases in the town of Leigh, Lancashire.

### Method

Persons considered to have definite clinical rheumatoid arthritis or who had a positive sheep-cell test in a survey of those between the age of 55 and 64 in a random sample of the town of Leigh (Kellgren and Lawrence, 1956) were revisited, and a list was made of surviving parents, siblings, and children over the age of 14. All those relatives living within a 10-mile radius of Leigh were then visited after an explanatory letter and questionnaire had been sent through the post. During this visit the questionnaire, which dealt with past and present rheumatic disorders, injury, and morning stiffness, was completed and arrangements were made for attendance at the centre for a detailed

clinical and radiological examination of the skeletal system and the collection of a sample of blood for the sheep-cell test.

At the same time a 1 in 30 sample of households in Leigh was taken from the electoral roll to serve as a control group. All those over the age of 14 years in these households were asked to attend the centre. The initial approach and the subsequent examination at the centre was identical in the rheumatoid families and the controls and appointments from each group were intermingled. Any persons found to have clinical rheumatoid arthritis or a positive sheep-cell test in the random sample were also used as *propositi* in the families study. To obviate undue radiological hazard a complete x-ray examination was considered undesirable in the younger age groups. The scheme adopted is shown below:

Age (yrs)	Parts X-Rayed
55+	Hands, feet, cervical spine, lumbar spine, knees, pelvis
35-54	Hands, feet, cervical spine, lumbar spine, knees
-34	Hands, feet, cervical spine

Antero-posterior views only were taken of the hands, feet, knees, and pelvis, and lateral views only of the cervical and lumbar spine.

Those persons who were unable or unwilling to come to the centre were examined at home. Owing to the limitations of portable equipment for home visits, x rays of the lumbar spine and pelvis had to be omitted in these cases, but the examination was otherwise identical with that carried out at the centre.

All x rays were read by one of us (J.S.L.), and were graded for osteoporosis, erosions, rheumatoid arthritis, and osteo-arthritis. The spinal films were also graded for disk degeneration. Five grades of severity\* were used: 0=None; 1=Doubtful; 2=Minimal; 3=Moderate; 4=Severe.

The system of reference numbers was so arranged that it was impossible for the examiner to tell, when reading the x rays, whether they belonged to the rheumatoid families or the controls, and no clinical or serological information was available to him at the time. Thus any bias on the part of the examiner can be excluded. This also applies to readings of the sheep-cell test, but not to the clinical examination.

**Completeness of Survey.**—Of 209 relatives of persons with rheumatoid arthritis living within the area (Table I), 183 (87 per cent.) were examined. Of 963 persons who comprised the random sample, 822 (85 per cent.) were examined. The response rate was thus similar in these two samples. The examination was complete in 95 per cent. of those examined in the rheumatoid families, but in 2 per cent. no blood test was available and in 3 per cent. x rays were refused. In the random sample, the corresponding figures were 95 per cent., 5 per cent., and 1 per cent.

**Composition of Rheumatoid Family Sample.**—The *propositi* were 67 in number (21 males and 43 females: Table I). The preponderance of females was practically confined to the group with clinical rheumatoid arthritis only. Those with a positive sheep-cell test, whether with or without clinical rheumatoid arthritis, were fairly equally distributed between the sexes. The age distribution of the *propositi* ranged between 43 and 78 years in the

\* For a more detailed definition of these gradings see Kellgren and Lawrence (1957).

TABLE I  
COMPLETENESS OF SURVEY

Sample		Total in Sample	Not Available or Refused All Examinations	Total Examined		Examinations Performed		
				No.	Percentage of Total Sample	Clinical, X Ray, and Blood Test	Clinical and X Ray Only	Clinical and Blood Test Only
Relatives of <i>Propositi</i>	Men	101	14	87	86	83	1	3
	Women	108	12	96	89	92	2	2
	Total	209	26	183	87	175	3	5
Random Sample	Men	474	65	409	86	391	13	5
	Women	489	76	413	84	384	26	3
	Total	963	141	822	85	775	39	8



TABLE II  
AGE AND SEX OF PROPOSITI

Sex .. ..	Male								Female								
Age (yrs) ..	-24	-34	-44	-54	-64	-74	75+	Total	-24	-34	-44	-54	-64	-74	75+	Total	Total
No. of Propositi	0	0	1	2	12	5	1	21	0	2	2	5	31	2	1	43	64

TABLE III  
AGE AND SEX OF RELATIVES OF PROPOSITI WITH VARIOUS GRADES OF  
CLINICAL AND SEROLOGICAL RHEUMATOID ARTHRITIS

Propositi					Numbers of Relatives, by sex and age (yrs)																
Sheep-Cell Agglutination Test	Clinical Rheumatoid Arthritis Grading	M.	F.	Total	Male								Female								Total
					-24	-34	-44	-54	-64	-74	75+	Total	-24	-34	-44	-54	-64	-74	75+	Total	
Negative	Moderate or Severe	3	5	8	3	1	0	1	6	2	0	13	2	1	1	2	2	0	10	23	
	Minimal	2	19	21	4	11	4	2	4	0	0	25	10	8	6	4	6	6	0	40	65
Positive	Moderate or Severe	4	6	10	2	3	1	1	3	2	0	12	0	4	0	5	3	3	0	15	27
	Minimal	2	2	4	1	2	1	3	2	1	0	10	0	1	0	3	1	0	1	6	16
	None or Doubtful	10	11	21	0	7	7	6	5	2	0	27	1	5	4	5	3	3	4	25	52
Totals .. ..		21	43	64	10	24	13	13	20	7	0	87	13	19	11	19	15	14	5	96	183

males and 26 and 75 years in females. As those between the ages of 55 and 64 were taken from a larger sample of the population, they form a relatively large group of the propoiti in both sexes and in no way reflect the true age distribution in the population (Table II).

Of the relatives examined, seven were parents, 95 siblings, and 81 offspring. The age and sex distribution of these relatives is as shown in Table III. In both sexes there were more young people in the families of those propoiti who had a negative sheep-cell agglutination test. The control group from the random sample was matched for decade and sex with the rheumatoid relatives, but within each decade and sex was chosen at random.

### Results

These have been assessed on the prevalence of clinical and radiological rheumatoid arthritis, on the sheep-cell titre, and finally on the American Rheumatism Association classification.

**Clinical Studies.**—Clinical rheumatoid arthritis (Grade 2-4) was encountered four times as often in the rheumatoid families as in the controls (Table IV, opposite).

The arthritis was also more severe, and the rheumatoid families had more persons with doubtful

rheumatoid arthritis, but past polyarthritis was not more frequent. The difference in the prevalence of Grade 2 to 4 rheumatoid arthritis between these two groups is highly significant ( $F = < 0.01$ ). Those families in which the propoiti had both a positive sheep-cell test and clinical rheumatoid arthritis had a greater prevalence than any of the others, 16 per cent. of the relatives of these persons having definite clinical disease. The families of those with a negative sheep-cell test had a lower prevalence, but the most striking contrast is with the relatives of those with Grade 3-4 disease and a negative test, none of whom had definite clinical disease. The numbers in this group, however, are small and the difference is thus not significant ( $P = 0.1$ ). The propoiti with a positive sheep-cell test but no clinical disease occupied an intermediate position, having one Grade 4 and one Grade 2 rheumatoid arthritic only in their families.

**Radiological Studies.**—Definite radiological evidence of rheumatoid arthritis (Table V, opposite) was found in 3 per cent. of the controls and in 7 per cent. of the rheumatoid families, the latter having more of the moderate or severe gradings ( $P = 0.06$ ). As in the clinical study, the relatives of those with both clinical rheumatoid arthritis and a positive sheep-cell test had more rheumatoid disease than

TABLE IV

PREVALENCE OF CLINICAL RHEUMATOID ARTHRITIS IN RELATIVES OF PROPOSITI AND IN CONTROLS

Propositi			Clinical Rheumatoid Arthritis Grading								Group Examined for Comparison
Sheep-cell Agglutination Test	Clinical Rheumatoid Arthritis Grading	No.	None	Past Poly-Arthritis Only	1 Doubtful	2 Minimal	3 Moderate	4 Severe	Total Examined	Grade 2-4 Minimal to Severe (Percentage of total)	
Negative	Moderate or or Severe ..	8	12	2	9	0	0	0	23	0	Relatives of Propositi
	Minimal ..	21	45	2	11	6	1	0	65	11	
Positive	Moderate or Severe ..	10	13	1	8	2	1	2	27	19	
	Minimal ..	4	7	3	4	1	1	0	16	13	
	None or Doubtful ..	21	34	0	16	1	0	1	52	4	
Total Propositi with Clinical Rheumatoid Arthritis ..		43	77	8	32	9	3	2	131	11	
Total Propositi with Positive Sheep-cell Agglutination Test ..		35	54	4	28	4	2	3	95	9	
Total ..		64	111	8	48	10	3	3	183	9	
—			152	12	15	3	0	1	183	2	Controls

TABLE V

PREVALENCE OF RADIOLOGICAL RHEUMATOID ARTHRITIS IN HANDS AND FEET IN RELATIVES OF PROPOSITI AND IN CONTROLS

Propositi			Radiological Rheumatoid Arthritis Grading								Group Examined for Comparison
Sheep-cell Agglutination Test	Clinical Rheumatoid Arthritis Grading	No.	None	Doubtful	Minimal	Moderate	Severe	Total X Rayed	Not X Rayed	Minimal to Severe (Percentage of total X Rayed)	
Negative	Moderate or Severe ..	8	18	5	0	0	0	23	0	0	Relatives of Propositi
	Minimal ..	21	53	8	1	0	0	62	3	2	
Positive	Moderate or Severe ..	10	14	7	2	0	3	26	1	19	
	Minimal ..	4	9	6	0	1	0	16	0	6	
	None or Doubtful ..	21	38	8	3	2	0	51	1	10	
Total Propositi with Clinical Rheumatoid Arthritis ..		43	94	26	3	1	3	127	4	6	
Total Propositi with Positive Sheep-cell Agglutination Test ..		35	61	21	5	3	3	93	2	12	
Total ..		64	132	34	6	3	3	178	5	7	
—			146	30	5	0	1	182	1	3	Controls

the remainder of the rheumatoid families. There were no definite radiological changes of rheumatoid arthritis in the families of those with Grade 3-4 rheumatoid arthritis and a negative test. There was, however, more radiological than clinical rheumatoid arthritis in the families of those with a positive sheep-cell test only,

these having three times as much as the controls. The difference is not significant ( $P=0.08$ ). There is, however, a very significant difference between the families of those with positive and negative sheep-cell tests, of whom 12 and 1 per cent. respectively had definite radiological evidence of rheumatoid arthritis ( $P=<0.01$ ). In fact, the sheep-cell

negative families had less than the controls. This might have been due to the large number of young people in the sero-negative families. When, however, those below 25 and over 65 years of age are removed from the rheumatoid family groups, the prevalence of radiological rheumatoid arthritis in the sero-positive and sero-negative families is 11 and 2 per cent. respectively and is thus still significant ( $P=0.01$ ).

**Sheep-Cell Test.**—The sheep-cell test similarly was positive in nearly three times as many of the rheumatoid relatives as of the controls (Table VI). The families of those with a negative sheep-cell test, however, showed no more positives than the controls. Relatives of the sero-positive cases on the other hand had four times as many ( $P=<0.01$ ). The families of propositi with a positive sheep-cell test without clinical disease had as many positives as the families of propositi with both clinical disease and a positive test. It should be noted that the difference between the rheumatoid families and controls is not limited to those with a titre of 1/32 or more, but applies to all titres down to a level of 1/8. When the relatives under 25 and over 65 years of age are removed from all groups, the proportion with a positive test in the sero-negative and sero-positive families becomes 8 and 20 per cent. respectively ( $P=0.06$ ).

**A.R.A. Classification.**—As a composite assessment of all the main features of rheumatoid arthritis, the A.R.A. classification (Ropes, Bennett,

Cobb, Jacox, and Jessar, 1956) has been used (Table VII, opposite). This reflects the findings in the previous Tables, though the differences tend to be less striking. The families of sero-negative rheumatoids show the same proportion with probable and definite rheumatoid arthritis as the controls, whereas the families of sero-positive rheumatoids have twice as much. As with clinical rheumatoid arthritis, the positives in the sero-negative families are limited to the families of those with Grade 2 clinical rheumatoid arthritis, and the families of those with a positive sheep-cell test without clinical disease have fewer positives than those with both clinical and serological evidence of rheumatoid arthritis.

**Osteo-Arthrosis.**—A relationship between rheumatoid arthritis and osteo-arthritis has been postulated from time to time, but was not confirmed in our studies of the 55 to 64 age group in Leigh (Kellgren and Lawrence, 1958). Difficulty may, however, have arisen from the opposing influence of two possible factors. On the one hand, the rheumatoid process may, by damaging articular cartilage predispose to degenerative change following minor trauma. On the other hand, it may, by preventing exercise, protect the joint from normal traumatic exposure. Where the rheumatoid process is severe, the latter effect will, except in the most hardy and determined patients, predominate. Where it is mild, and particularly if it is sub-clinical, the former effect will be more important. The present

TABLE VI  
SHEEP-CELL AGGLUTINATION TEST TITRE DISTRIBUTION IN RELATIVES OF PROPOSITI  
AND IN CONTROLS

Propositi			Sheep-cell Agglutination Test Titre										Group Examined for Comparison	
Sheep-cell Agglutination Test	Clinical Rheumatoid Arthritis Grading	No.	Negative				Positive				Total Tested	Not Tested		Positives (Percentage of Total tested)
			1/<4	1/4	1/8	1/16	1/32	1/64	1/128	1/256				
Negative	Moderate or Severe ..	8	16	2	2	0	1	1	0	0	22	1	9 } 5 } 6	Relatives of Propositi
	Minimal ..	21	27	11	18	5	1	0	1	1	64	1		
Positive	Moderate or Severe ..	10	11	4	3	2	3	2	1	1	27	0	26	
	Minimal ..	4	11	1	2	1	0	0	0	0	15	1	0	
	None or Doubtful ..	21	25	10	3	2	8	3	0	1	52	0	23	
Total Propositi with Clinical Rheumatoid Arthritis ..		43	65	18	25	8	5	3	2	2	128	3	9	
Total Propositi with Positive Sheep-cell Agglutination Test .. ..		35	47	15	8	5	11	5	1	2	94	1	20	
Total .. ..		64	90	28	28	10	13	6	2	3	180	3	13	
—			100	35	23	9	6	0	1	2	176	7	5	Controls

TABLE VII  
AMERICAN RHEUMATISM ASSOCIATION CLASSIFICATION APPLIED TO RELATIVES  
OF PROPOSITI AND TO CONTROLS

Propositi			A.R.A. Grading						Group Examined for Comparison
Sheep-cell Agglutination Test	Clinical Rheumatoid Arthritis Grading	No.	None	Possible	Probable	Definite	Total	Probable + Definite (Percentage of total)	
Negative	Moderate or Severe ..	8	18	5	0	0	23	0	Relatives of Propositi
	Minimal .. ..	21	56	5	4	0	65	6	
Positive	Moderate or Severe ..	10	18	4	2	3	27	18	
	Minimal .. ..	4	13	1	2	0	16	13	
	None or Doubtful ..	21	42	7	2	1	52	6	
Total Propositi with Clinical Rheumatoid Arthritis ..			43	105	15	8	3	131	8
Total Propositi with Positive Sheep-cell Agglutination Test .. ..			35	73	12	6	4	95	11
Total .. ..			64	147	22	10	4	183	8
—			152	22	7	2	183	5	Controls

TABLE VIII  
PREVALENCE OF RADIOLOGICAL MULTIPLE OSTEO-ARTHRITIS IN RELATIVES OF  
PROPOSITI AND IN CONTROLS

Propositi			No. of Joints Affected by Radiological Osteo-Arthritis (Minimal to Severe)													Group Examined for Comparison
Sheep-cell Agglutination Test	Clinical Rheumatoid Arthritis Grading	No.	0	1	2	3	4	5	6	7	8	9+	Total X Rayed	Not X Rayed	5+ (percentage of total x rayed)	
Negative	Moderate or Severe ..	8	10	5	1	2	1	3	0	0	1	0	23	0	17	Relatives of Propositi
	Minimal .. ..	21	38	10	4	2	2	3	2	0	0	0	61	4	8	
Positive	Moderate or Severe ..	10	12	5	2	3	1	0	0	2	0	1	26	1	12	
	Minimal .. ..	4	6	2	2	0	3	1	1	0	0	0	15	1	13	
	None or Doubtful ..	21	20	12	7	5	4	1	0	1	1	0	51	1	6	
Positive or Negative	Minimal to Severe ..	43	66	22	9	7	7	7	3	2	1	1	125	6	11	
Positive	None to Severe ..	35	38	19	11	8	8	2	1	3	1	1	92	3	9	
Total .. ..			64	86	34	16	12	11	8	3	3	2	176	7	10	
—			93	29	19	10	16	6	4	1	1	1	180	3	7	Controls

study offers a useful opportunity to test the latter hypothesis. If it is correct a higher proportion of persons with osteo-arthritis, and particularly with multiple osteo-arthritis, would be expected in the rheumatoid families. As shown in Table VIII this is not the case, the sero-positive families having no more multiple osteo-arthritis than the sero-negative families and not significantly more than the controls. Only the families of moderate to severe sero-negative propositi have more than twice as much multiple osteo-arthritis as the controls, but the numbers in this group are too small to give a significant difference.

*Sheep-Cell Titre in Propositi.*—So far the propositi have been divided into those having a positive test at a serum dilution of 1/32 and those not producing agglutination at this level. In view of the somewhat raised prevalence of rheumatoid arthritis in the families of those with Grade 2 clinical rheumatoid arthritis and a negative test, it may be considered whether in minimal rheumatoid arthritis a lower titre may not exclude the patient from the sero-positive group. It should be borne in mind that only a single test was made on each propositus, so that no allowance is made for transient fluctuations in the titre.



TABLE IX

PREVALENCE OF CLINICAL, RADIOLOGICAL, AND SEROLOGICAL RHEUMATOID ARTHRITIS IN RELATIVES OF PROPOSITI IN RELATION TO SHEEP-CELL AGGLUTINATION TEST TITRE IN PROPOSITI

Propositi			Relatives						
Sheep-cell Agglutination Test Titre		No.	Total No.	Definite Clinical Rheumatoid Arthritis		Definite Radiological Rheumatoid Arthritis in Hands and Feet		Sheep-cell Agglutination Test Positive	
				No.	Percentage of Total	No.	Percentage of Total X Rayed	No.	Percentage of Total Tested
Negative	1 : <4	19	54	4	7	0	0	4	7
	1 : 4	7	15	3	9	0	3	1	3
	1 : 8	1	5	0		0		0	
	1 : 16	2	14	0		1		0	
Positive	1 : 32	12	34	1	6	1	9	9	21
	1 : 64	6	13	2		3		1	
	1 : 128	6	18	1	13	2	15	4	25
	1 : 256	7	22	3		3		4	
	1 : 512	4	8	2		2		1	
Total .. ..		64	183	16	9	12	7	24	13

In Table IX they are classified by sheep-cell titre, regardless of the presence of clinical disease. The families of those with a titre of 1 : 4 to 1 : 16 showed no constant difference from the families without agglutination. Above this level there was an increase of both radiological and serological evidence of rheumatoid arthritis in relatives. At a titre of 1 : 128 and above, there was a further increase of radiological and serological positives and clinical disease was also more prevalent. The differences between the last two levels, however, are small and may well be due to chance variation in the families.

### Discussion

From the findings in this study it is clear that there is a strong familial trend in rheumatoid arthritis. It is first necessary to consider whether this is hereditary or environmental. If the latter, it would be expected that unrelated members of the rheumatoid households would show a high prevalence. Of the spouses of the propositi in this study seventeen were examined. None of these showed clinical or radiological evidence of rheumatoid arthritis and only one had a positive sheep-cell test. The prevalence of positive tests in the population of this age group was 5 per cent., so that a single positive result might well be due to chance. An examination of the material available in the rheumatic complaints study made in Leigh in 1950, in which all persons over 15 years of age in 1,393 households were seen, revealed the same prevalence of rheumatoid arthritis in the households of those with rheumatoid arthritis as in the total sample. It would thus seem unlikely that home environment

plays an important part or that it could explain the high prevalence which has been discovered in the relatives of persons with rheumatoid arthritis in this study. On both radiological and serological grounds there is sharp division between the families of sero-negative and sero-positive propositi. Only on the clinical assessment do the sero-negative families have more rheumatoid arthritis than the controls, and of these only the families of Grade 2 propositi contain persons with rheumatoid arthritis. Of the seven relatives graded as having definite clinical rheumatoid arthritis in this group, one had moderately severe disease confirmed radiologically. The remaining six had minimal signs, generally with symptoms in the past only and without radiological or serological confirmation. All had radiological evidence of osteo-arthritis in one or more groups of joints, and it may be considered whether confusion has arisen between rheumatoid arthritis and primary generalized osteo-arthritis in the relatives and possibly also in the propositi, who similarly all had radiological evidence of osteo-arthritis in one or more joints. It should be mentioned that there is evidence of a strong hereditary factor in primary generalized osteo-arthritis (Kellgren and Lawrence, 1958). The other possibility, that the propositi had sero-positive disease which had become sero-negative, appeared unlikely as a marginal titre was encountered only once and most had a negative test even with undiluted serum.

Determination of the mode of inheritance presents some difficulty owing to the low expressivity of the disease in the lower age groups. Though a positive sheep-cell test may serve as a useful index of the presence of the abnormal gene, a negative test does

not indicate its absence, since the test is not positive at birth but develops in later life, commonly with or after the onset of symptoms. For example, in those aged 65 or over in the sero-positive families, a positive sheep-cell agglutination test occurred in 38 per cent. compared with 16 per cent. in those under 65. Of the controls aged 65 or over, 13 per cent. had a positive test. If this number is deducted from the sero-positive families, a proportion of 25 per cent. with a positive test remains. This is the proportion of siblings which would be expected to show the abnormality if the condition were a recessive. If the 13 per cent. of controls with a positive test in this age group represent the total persons who are homozygous for the abnormality, the gene frequency would be  $\sqrt{0.13}=0.36$  or roughly one in three of the population. This is based on the assumption that all those who are homozygous for the abnormal gene will have developed a positive sheep-cell agglutination test by the age of 65 years.

Cobb, Warren, Thompson, and Ciocco (1954) have produced evidence that morning stiffness is an important manifestation of rheumatoid arthritis. It is of interest, therefore, to investigate the frequency of this symptom in rheumatoid families and in particular to make a comparison between sero-positive and sero-negative families. With this in view a question on morning stiffness was included in the examination of all respondents. In fact, only the families of those with clinical rheumatoid arthritis plus a positive sheep-cell agglutination test had appreciably more morning stiffness than the controls (Table X). Of the members of these families, 35 per cent. complained of morning stiff-

ness compared with 25 per cent. in the controls, and 20 per cent. in the sero-negative families ( $P=0.07$ ). Though not conclusive, these figures suggest that morning stiffness is a feature rather of sero-positive rheumatoid arthritis than of rheumatoid disease as a whole. It should be noted that both morning stiffness and clinical rheumatoid arthritis are less frequent in the relatives of sero-positive propositi without clinical disease than in the relatives of those with clinical rheumatoid arthritis. The possibility that a second allele may be concerned with the clinical manifestations of the disease cannot, therefore, be excluded.

### Summary

(1) A series of 183 relatives (parents, siblings, and children) of persons with either clinical rheumatoid arthritis or a positive sheep-cell test was examined clinically, radiologically, and serologically, and compared with a control group matched by age and sex. The propositi and the controls were taken from random samples of the population of a Lancashire town.

(2) Clinical, radiological, and serological evidence of rheumatoid arthritis was encountered four times more frequently in the families of those with a positive sheep-cell test than in the controls. The families of sero-negative propositi showed no more radiological or serological evidence of the disease than the controls, but had more clinical rheumatoid arthritis. This clinical disease was of minimal severity and was found only in the relatives of propositi who had themselves minimal clinical rheumatoid arthritis. Both relatives and propositi

TABLE X  
PREVALENCE OF MORNING STIFFNESS IN RELATIVES OF PROPOSITI AND IN CONTROLS

Propositi			Morning Stiffness				Group Examined for Comparison
Sheep-cell Agglutination Test	Clinical Rheumatoid Arthritis Grading	No.	Present	Total Stated	Not Stated	Present (percentage of total stated)	
Negative	Moderate or Severe ..	8	6	21	2	29	Relatives of Propositi
	Minimal .. ..	21	11	64	1	17	
Positive	Moderate or Severe ..	10	10	26	1	38	
	Minimal .. ..	4	5	15	1	33	
	None or Doubtful ..	21	11	51	1	22	
Total Propositi with Clinical Rheumatoid Arthritis		43	32	125	5	25	
Total Propositi with Positive Sheep-cell Agglutination Test ..		35	26	92	3	28	
Total .. ..		64	43	177	6	24	
—			45	177	6	25	Controls

in this group had a high prevalence of multiple osteo-arthritis.

(3) The mode of inheritance of sero-positive rheumatoid arthritis is discussed.

We wish to express our thanks to Professor J. H. Kellgren for advice on the planning and execution of this survey and to the people of Leigh for generously taking part. We are indebted to the Pneumoconiosis Research Unit (Cardiff) for technical assistance and the loan of equipment, and to Prof. J. S. Penrose and Mr. M. G. Bulmer for advice on the genetic aspects.

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#### Etudes génétiques de l'arthrite rhumatoïdale

##### RÉSUMÉ

(1) Une série de 183 parents (pères, mères, frères, soeurs et enfants) des personnes, soit atteintes d'arthrite rhumatoïdale clinique, soit accusant une réaction d'agglutination de globules de mouton positive, furent examinés du point de vue clinique, radiologique et sérologique, et comparés à un groupe de témoins d'âge et de sexe équivalent. Les sujets et les témoins furent

choisis au hasard parmi les habitants d'une ville de Lancashire.

(2) Preuves cliniques, radiologiques et sérologiques d'arthrite rhumatoïdale furent rencontrées quatre fois plus souvent dans les familles des sujets ayant une réaction d'agglutination positive que chez les témoins. Dans les familles des sujets séro-négatifs la fréquence des signes radiologiques ou sérologiques de la maladie ne fut pas supérieure à celle des témoins, mais l'arthrite rhumatoïdale clinique fut plus fréquente. Cette arthrite clinique fut peu grave et n'existait que chez des parents des sujets eux mêmes atteints d'une arthrite très bénigne. Dans ce groupe, aussi bien chez les parents que chez les sujets, on trouva beaucoup de cas d'ostéo-arthrose multiple.

(3) On discute le mode de transmission héréditaire de l'arthrite rhumatoïdale séro-positive.

#### Estudios genéticos de la artritis reumatoide

##### SUMARIO

(1) Una serie de 183 parientes (padres, hermanos e hijos, de ambos sexos) de sujetos sea con artritis reumatoide clínica, sea con una reacción de aglutinación de glóbulos de oveja positiva, fué examinada clínica, radiológica y serológicamente y comparada con un grupo de testigos de edad y sexo correspondientes. Los sujetos y los testigos fueron escogidos al azar en una ciudad de Lancashire.

(2) Pruebas clínicas, radiológicas y serológicas de artritis reumatoide fueron encontradas cuatro veces más a menudo en las familias de los sujetos con la reacción de aglutinación positiva que en los testigos. En las familias de los sujetos sero-negativos, la frecuencia de los signos radiológicos o serológicos de la enfermedad no fué superior a la en los testigos, pero la artritis reumatoide clínica fué más frecuente. Esta artritis clínica fué benigna y existió sólo en los parientes de los sujetos cuya artritis fué también benigna. En este grupo, tanto en los parientes como en los sujetos, hubo muchos casos de osteo-artrosis multiple.

(3) Se discute el modo de transmisión hereditaria de la artritis reumatoide sero-positiva.

## ARTHRITIS ASSOCIATED WITH ULCERATIVE COLITIS

### A CLINICAL AND PATHOLOGICAL STUDY

BY

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The arthritis associated with ulcerative colitis has not been fully delineated, although Hench (1935) gave an excellent short characterization. Recent textbooks on arthritis omit mention of it (Copeman, 1955; Comroe, 1953) or give it a few lines only (Fletcher, 1951). In the comprehensive American and English language reviews published in the *Annals of Internal Medicine* by the American Rheumatism Association, no mention of it has been made since 1940 (Hench and others, 1940, 1941, 1948; Robinson and others, 1953, 1956), nor is it classified as such in the "Standard Nomenclature of Disease" approved by the American Rheumatism Association. This is possibly because it is thought to be merely rheumatoid arthritis occurring in ulcerative colitis, rather than a special entity (Hench and others, 1936). With the emergence of a nearly specific diagnostic test and more knowledge about this group of diseases, it seems opportune to review this problem again in the light of fourteen cases seen personally at the Special Unit for Juvenile Rheumatism, Canadian Red Cross Memorial Hospital and at the Postgraduate School, over the last 11 years, together with eight cases seen with Dr. Kellock at the Central Middlesex Hospital, and eight cases seen with Dr. Coghill at the West Middlesex Hospital. Data from seven other cases at these hospitals is also included, although these cases were not seen personally, making a total of 37 patients.

#### Material and Methods

Ulcerative colitis was diagnosed on the basis of a characteristic pathological, radiological, or sigmoidoscopic appearance, plus a compatible clinical history, including diarrhoea. The Rose-Waaler differential agglutination of sensitized sheep cells "D.A.T." has been carried out in its original form by Dr. Frances Scott at Taplow (Scott, 1952).

#### Clinical Investigations

##### **Incidence of Joint Manifestations in Ulcerative Colitis**

Ulcerative colitis is a comparatively uncommon disease and nowadays tends to be concentrated at hospitals where an active interest is taken in the special long-term medical, psychological, social, and surgical problems involved. The number of fresh in-patients diagnosed per year and fulfilling the above criteria during the last 10 to 11 years at Taplow, 1947-1956, and at Hammersmith, 1946-1956, was 38 (Taplow) and 71 (Hammersmith) out of a total turnover of 4,000 and 10,000 admissions per year respectively. This is a figure comparable with the 10.9 cases of ulcerative colitis per 10,000 admissions cited by Melrose (1955) from 23 teaching hospitals in Great Britain.

Arthritis and arthralgia occurred in only a few of these 109 patients. Thus, of the total 38 Taplow patients specifically referred to the general medical and surgical consultant staff with symptoms of colitis, only four showed or later developed joint signs and only two complained of arthralgia in a total mean period from onset to follow-up of 6.7 years. During the same period two patients were referred primarily because of their joints. At Hammersmith twelve patients had arthritis and four more had arthralgia only, out of the total of 71 seen between 1946 and 1956.

Thus these figures for joint involvement in ulcerative colitis considerably exceed most of those quoted in the literature (Table I, overleaf), but it is still a comparatively small proportion of the whole.

It is somewhat greater than the 2.4 per cent. estimated by Kellgren, Lawrence, and Aitken-Swan (1953) or the 7.8 per cent. estimated by Kellgren and Lawrence (1956) for the incidence of rheumatoid arthritis in adults based on survey work.



TABLE I  
INCIDENCE OF ARTHRITIS IN ULCERATIVE COLITIS

Place of Investigation	Authors	Date	Total No. of Cases	Percentage with Arthritis
Mayo Clinic .. ..	Bargen	Cited by Hench, 1935	1,500	4
Oxford .. ..	Rice-Oxley and Truelove	1950	129	5.4
Mayo Clinic .. ..	Sloan, Bargen, and Gage	1950	2,000	7.7
New York, Montefiore	Brown, Kasich, and Weingarten	1951	147	7.5
Minneapolis .. ..	Dennis and Karlson	1952	267	7.1
Birmingham .. ..	Brooke	1956	131	13
Boston .. ..	Kirsner, Palmer, Maimon, and Ricketts	1948	100	8
Boston .. ..	Kirsner, Sklar, and Palmer	1957	180	22

### Age and Sex Incidence

Of the 37 patients reviewed here (Table II, opposite), 28 were females (76 per cent.) compared with a sex ratio of 68 F./41 M. for ulcerative colitis as a whole at Taplow and Hammersmith (62 per cent.), and 62 per cent. in the recent series of Cullinan and MacDougall (1957), and a ratio of 2 : 1 (64 per cent. females) for rheumatoid arthritis (Lewis-Faning, 1950).

The mean age at onset of the ulcerative colitis was 26.7 years (male) and 32.9 years female (range 13 to 44 and 8 to 67 respectively). The age at onset of the arthritis was 10 to 48 yrs in the nine males (mean 26.3) which was slightly less than the range of 8 to 67 in the 28 females (mean 34.8).

Ulcerative colitis preceded arthritis in seventeen patients (range 16 years to 1 week; mean 4 yrs 7 mths); the onset was simultaneous in four patients, and in seven the arthritis preceded the colitis by intervals of from 8 yrs to 7 wks (mean 36 mths). All these groups included children, and also patients

with remissions of joint symptoms such as are only rarely seen in ordinary rheumatoid arthritis.

In previously reported cases, arthritis has been known to precede colitis by as much as 5 years (Comfort, Bargen, and Morlock, 1938).

### Special Aspects of Joint Involvement

(a) *Joints Involved.*—The joints involved most frequently were the knees and ankles. Finger joints were not so frequently affected as in rheumatoid arthritis, but involvement of the distal and proximal interphalangeal toe joints was seen in four patients (e.g. Case 8, Table II, Fig. 1a, b, c). In our experience the proximal and distal interphalangeal joints of the toes are very seldom involved in typical rheumatoid arthritis; when they are involved a search should be conducted for signs of psoriasis, colitis, or Reiter's syndrome. In Case 2 (Table II), suspected of having rheumatic fever on account of a migratory polyarthritis with effusion into one knee and a high fever, this feature led us to suspect

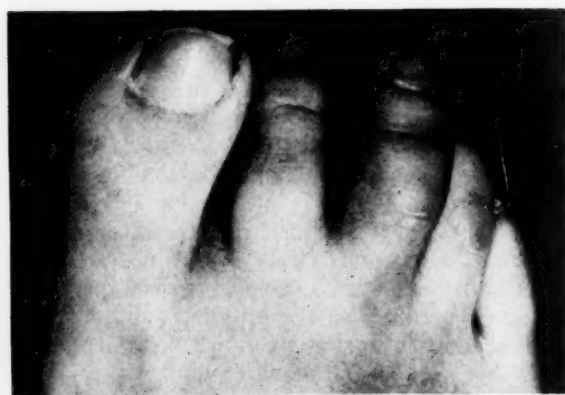


Fig. 1. Case 8 (a).—Toe involvement in first attack of acute arthritis 10 years after onset of ulcerative colitis.



(b).—X ray of foot at onset of arthritis, showing periostitis and metatarsal head erosion.



(c).—X ray of foot 7 years after acute arthritis, showing disappearance of periostitis and healed erosion.

TABLE II  
PARTICULARS OF 37 CASES OF ULCERATIVE COLITIS

Case No.	When First Seen				E.N.	-Ectomy (EC) -Ostomy (OS)  Operation	Follow-up Examination			Differential Agglutination Test
	Sex	Age (yrs)	Duration of				Yrs from Date of First Observation	Joint Residua at Last Examination		
			Joint Involvement	Colitis				Clinical	Radio-logical	
1	M	16	6 yrs	(8 mths later)	0	—	3	0	+	1 : 4
2	F	18	1 mth	1 mth	0	—	4	0	0	1 : 2
3	F	38	3 mths	21 mths	0	-OS -EC	6	+	+	1 : 2
4	M	35	14 mths	18 mths	0	-OS	(Died after 2 yrs)	0	+	—
5	F	24	(1 yr later)	6 mths	0	-OS -EC	7	+	0	1 : 2
6	F	57	1 mth	4 mths	0	-OS	10	+	0	1 : 4
7	F	36	5 mths	19 mths	0	—	1	+	+	1 : 2
8	F	44	6 mths	10 yrs	0	—	7	0	+	1 : 2
9	F	29	18 mths	5 yrs	0	—	9	+	+	—
10	F	54	3 yrs	4 yrs	0	—	(Died after 5 yrs)	0	0	—
11	F	57	14 yrs	14 yrs	+	—	Not traced	0	0	—
12	F	44	5 yrs	5 yrs	0	—	Not traced	+	+	—
13	F	14	6 yrs	6 yrs	0	—	6	+	+	1 : 2
14	F	42	18 yrs	23 yrs	+	—	9	+	+	1 : 2
15	M	13	(2 mths later)	1 mth	+	—	3	0	0	1 : 8
16	M	13	1 yr	?1 yr	0	—	4	0	0	1 : 8
17	F	12	(7 mths later)	3 wks	0	Partial -EC	Not traced	0	0	—
18	F	46	3 yrs +	10 mths	0	-EC	(Died after 4 mths)	+	0	—
19	F	35	4 wks	11 yrs	0	—	6 mths	+	0	1 : 2
20	M	24	9 days	(12 mths later)	0	—	1	0	+	1 : 4
21	F	27	1 mth	4 mths	+	-EC	5	0	+	1 : 2
22	F	25	4 mths	13 yrs	+	-OS	1	0	0	1 : 1
23	F	53	2 wks	16 yrs	+	—	1	0	0	1 : 2
24	F	52	2 yrs	18 mths	0	-OS	9	+	+	1 : 64
25	F	40	7 mths	1 mth	0	—	2	0	0	1 : 1
26	F	21	2 days	3 wks	+	-EC	5	0	0	1 : 2
27	F	47	(6 yrs later)	3 yrs	0	—	7	0	0	1 : 2
28	F	36	1 mth	4 mths	0	—	5	+	+	—
29	M	35	1 yr	7 yrs	0	-EC	5	0	0	—
30	F	33	(8 mths later)	5 wks	0	-OS	1	+	+	1 : 4
31	F	22	10 yrs	10 yrs	0	(Partial -EC)	4	0	0	1 : 8
32	F	67	1 wk	1-2 wks	0	—	3	0	0	1 : 4
33	M	44	(4 yrs later)	1-2 wks	0	—	12	+	+	1 : 2
34	F	51	8 yrs	2 wks	0	—	10	+	+	1 : 256
35	M	50	7 yrs	8 yrs	0	—	3	+	+	1 : 2
36	M	22	2-3 wks	18 mths	+	—	6	0	0	1 : 1,024
37	F	36	1 mth	(3 mths later)	0	—	7	0	0	1 : 4

ulcerative colitis before any obvious diarrhoea had occurred, and the diagnosis was confirmed at this stage by barium enema. In the following 4 years the patient had three more attacks of arthritis with severe colitic symptoms in two of them, but she is now well and has no residua. When arthritis resolves, as it does not infrequently, leaving no clinical residua, x-ray examination may reveal small residual healed erosions, such as are seen in Fig. 1(c).

Sacro-iliac involvement was seen in six patients, in none of whom was there limitation of back movement. We were unable to distinguish this change radiologically from that of ankylosing spondylitis. One of these patients also had psoriasis, but this antedated the colitis by 11 years and the arthritis by 15 years. Although the proximal interphalangeal joints of the fingers were involved, the distal joints of the toes were not affected and the arthritis subsided with the colitis; the psoriasis, however, persisted. In Cases 1 and 13 (Table II) the sub-Achilles bursa was involved, which is more characteristic of Reiter's disease or ankylosing spondylitis (Bywaters, 1954), though it is sometimes seen in rheumatoid arthritis. Both showed sacro-

iliac involvement (Fig. 2). In Case 13 erosions of the ischia and the great trochanters (symptomless) and pseudo-cystic lesions in the acetabular margins were seen radiologically (Fig. 3, opposite), and in the neck there was an anterior erosion of the third cervical vertebra (Fig. 4, opposite) of the type described by Romanus and Ydén (1955).

(b) *Course and Clinical Pattern of Joint Involvement.*—More characteristic than the particular joints affected was the course and clinical pattern of joint involvement. This, in most instances, was a recurrent mild synovitis, attacking first one or two and then more joints, subsiding in some as it affected others. Because of this the disease was difficult to differentiate from rheumatic fever, and in fact some of our cases were initially labelled as such. However, the synovitis tended to recur, localizing in one or two of the joints that had been affected longest. The migratory and recurrent nature of the polyarthritis is well illustrated in Case 13, in which the areas affected were those usually seen in ankylosing spondylitis. In this particular case a remarkable feature was the excellent general condition despite a persistently high



Fig. 2.—Case 1, erosion and fusion of sacro-iliac joints.



Fig. 3.—Case 13, pseudo-cystic lesions in acetabular and ischial margins seen in course of barium enema while the patient was symptom-free.



1954 1957

Fig. 4.—Case 13, anterior erosion of third cervical vertebra progressing between 1954 and 1957.

erythrocyte sedimentation rate, marked changes in the barium enema (Fig. 5), and minimal residua (slight limitation of dorsiflexion of the right wrist and extension of the neck) some 12 years from the onset of the disease.



Fig. 5.—Case 13, barium enema during symptomless period.



Remission might occur, usually coincident with improvement in the gut symptoms. Irreversible changes following cartilage erosion occurred in seventeen of the cases personally seen, but in four these changes were radiological only. In four cases there was slight clinical limitation of an elbow or wrist joint without radiological change. In only four patients were there gross changes such as are described in textbooks as "rheumatoid", and in two of these (Cases 14 and 35, Table II) the course was not completely typical for rheumatoid arthritis.

One of the latter two (Case 14) showed complete subsidence of the arthritis between the attacks of diarrhoea, with numerous exacerbations over a period of many years before irreversible changes occurred. Even then, the course was characterized by the exacerbation of arthritis accompanying increased gut activity, with erythema nodosum on one occasion (Fig. 6) and a rash resembling that seen in Still's disease on another. Sclerosis of the sacro-iliac joints occurred in addition to erosions seen in the hand x rays.



Fig. 6.—Case 14, erythema nodosum occurring with an acute exacerbation 24 years after first attack of arthritis and 27 years after onset of ulcerative colitis.

The second (Case 35) developed a mild arthritis one year after the onset of colitis followed by a severe generalized polyarthritis 2 years later, preceding an acute exacerbation of diarrhoea. Both conditions slowly improved and 6 years later this patient is in excellent general health, but he has some limitation of movement of both elbows and such severe hip residua that an arthrodesis has been performed on one side and an arthroplasty on the

other. The hands appeared normal on clinical examination despite radiological changes (Fig. 7).

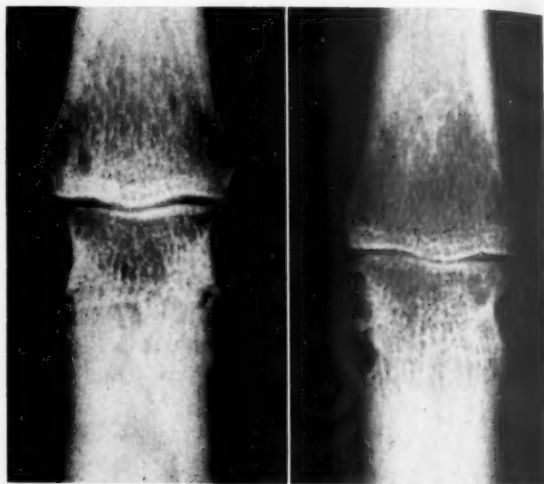


Fig. 7.—Case 35, x ray of left third and fourth proximal interphalangeal joints showing radiological change without clinical residua.

In neither case was the differential agglutination test ever positive.

Two cases, both women, appeared to have typical rheumatoid arthritis, in that there was gross symmetrical involvement of the hands, feet, knees, shoulders, and elbows, with radiological evidence of erosions before the onset of the colitis. In neither case was the development of colitis associated with any exacerbation of joint symptoms, and no remission of joint symptoms followed spontaneous remission of the colitis in one and total colectomy in the other; in fact neither showed any tendency to remission of arthritis at any time. Both cases showed tendon involvement, one had typical rheumatoid nodules, and in both the differential agglutination test was strongly positive. We regard these two patients as having two diseases concurrently.

(c) *Radiological Findings.*—In many cases these do not differ from those of rheumatoid arthritis. In the early stages, osteoporosis only is seen, and since remission so frequently occurs, this completely reversible change often disappears. Later, with severe or longer maintained inflammation, periostitis may be seen (Fig. 1b) eventually resolving or welding with bone, and finally erosions occur. These may be slight and when healing occurs only slight defects may be left (Fig. 1c) or erosion may be severe enough to lead to complete loss of cartilage and ankylosis as in Case 3 (Table II; Fig. 8, opposite).

In patients with backache, x rays of the pelvis were taken, and in other cases, although no such

Fig. 8.  
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Fig. 8.—Case 3, x ray of wrist showing progression of changes and periostitis from 1952 to 1954, despite remission of the disease.

examination was made, sacro-iliac lesions were looked for in x rays of the pelvis taken in the course of barium enema studies and could occasionally be discerned; changes seen in the neck, trochanter, and ischial ramus of Case 13 are illustrated in Figs 3 and 4, and are indistinguishable from those which occur in ankylosing spondylitis.

(d) *Histological Appearances.*—The synovial membrane (three patients) is similar to that of rheumatoid arthritis, and not very different from that of the inflamed gut. There is synovial cell hyperplasia or loss of lining cells; in mild cases such as Case 13, a few lymphocytes and an occasional plasma cell and polymorph are seen in the subjacent membrane (Fig. 9). With more severe involvement, these changes are more pronounced, with much fibroblast proliferation and increased vascularity, with fibrin incorporated into the surface and more polymorphonuclears, lymphocytes, and plasma cells (Case 14, Fig. 10).

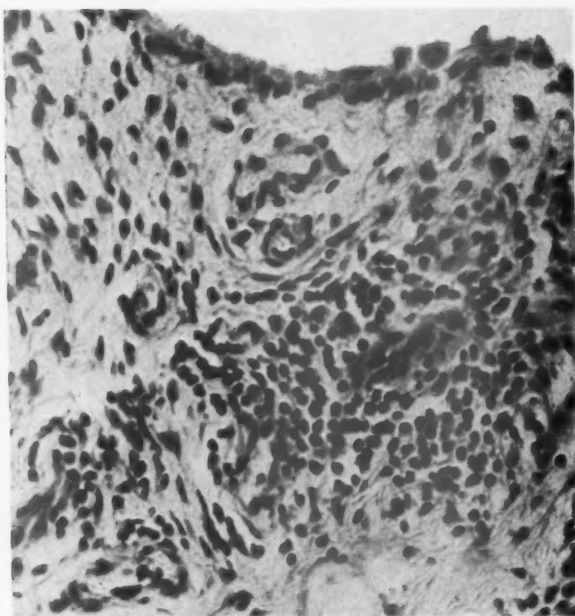


Fig. 9.—Case 13, synovial membrane of right wrist 3½ weeks after onset of swelling. Haematoxylin and eosin  $\times 240$ .

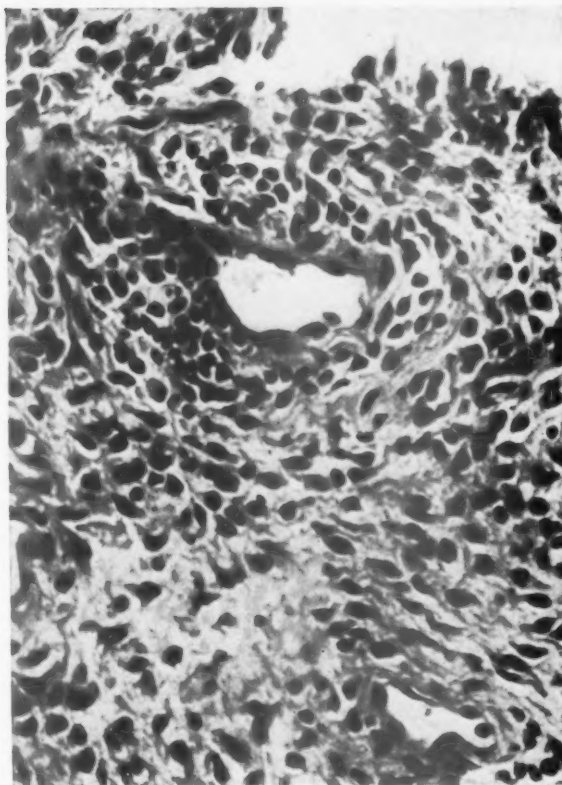


Fig. 10.—Case 14, synovial membrane, showing plasma cells, lymphocytes, and synovial cell hyperplasia. Haematoxylin and eosin  $\times 285$ .



Fig. 11.—Case 14, synovial membrane, showing bone detritus. Haematoxylin and eosin  $\times 135$ .

In places the cartilage can be seen to be eroded, and fragments of necrotic cartilage and bone can be seen embedded in the synovial membrane (Case 14, Fig. 11). In one case, besides these changes, there were some epithelioid-looking cell collections but no caseation (Case 16, Table II, Fig. 12, opposite); both staining and culture for tuberculosis were negative.

(e) *Serological Findings.*—The Rose-Waaler test has been persistently negative in 25 out of 29 patients tested. In one (Case 15, Table II) it was positive on one occasion, but on retesting 3 weeks later it was within normal limits (1 : 8).

In only one case was a positive Rose test found in the complete absence of joint symptoms and residua. The two cases in which the differential agglutination test was persistently positive resemble classical rheumatoid arthritis, with tendon involvement in both and in one nodule formation.

The erythrocyte sedimentation rate was usually raised during the active episodes to high levels (e.g. 60-126 mm./hr Westergren) as might be expected with the large amount of gut affected. In

remission, the erythrocyte sedimentation rate might be normal (e.g. Case 16, Fig. 13, opposite) or raised despite absence of either gut or joint complaints. Other investigations were either negative or non-specific (e.g. electrophoretic protein studies, agglutinations for Typhi- and Paratyphi A and B, Flexner, etc.).

(f) *Synovial Fluid.*—In ulcerative colitis patients this shows considerable variation (Table III, overleaf). In general it is not very different from that found in patients with mild rheumatoid arthritis, as Ropes and Bauer (1953) have pointed out on the basis of fluids from up to five joints. We found in severely affected patients a rather higher maximal cell count than that reported by Ropes and Bauer (11,800 per c.mm.), and in none of our cases was the majority of cells present other than polymorphonuclear. In most of our cases the protein content was low and fitted in well with the clinical finding of mild migratory synovitis, but the relative viscosity was unexpectedly low rather than high. These two characteristics generally have an inverse relationship: a high polymorphonuclear cell count, low



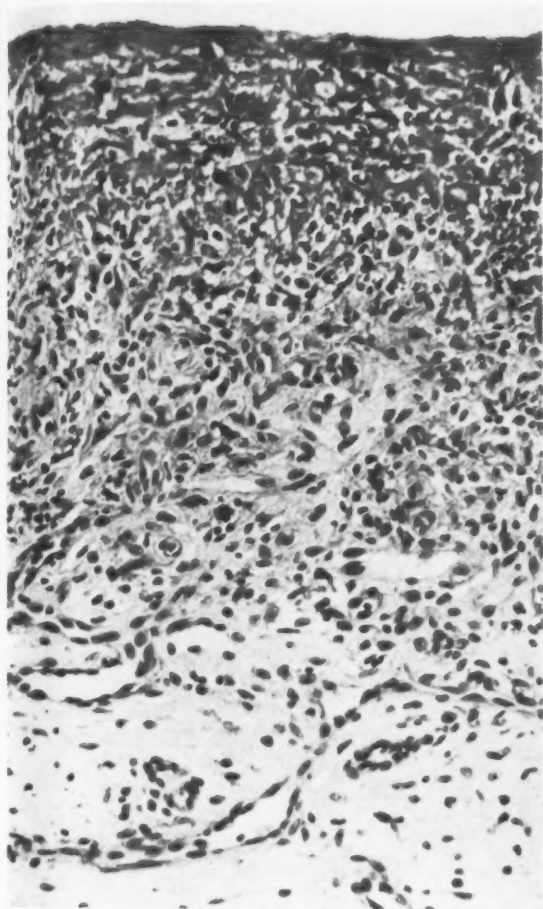


Fig. 12.—Case 16, synovial membrane, showing surface fibrin and epithelioid cell clusters but no caseation. Haematoxylin and eosin  $\times 200$ .

relative viscosity, and high protein content usually accompany severe and chronic types of arthritis, and are accompanied by a low glucose content and a cloudy or granular acetic acid precipitate.

### Diagnosis

The most common conditions from which this disease requires to be differentiated are rheumatic fever, rheumatoid arthritis, and ankylosing spondylitis, while Reiter's disease with diarrhoea, psoriatic arthritis, and polyarteritis nodosa may occasionally be mimicked. The difficulties in diagnosis are well illustrated by Case 16 (Table II), who developed arthritis while on treatment for what was thought to be *tabes mesenterica*. Not until 2 years later was a diagnosis of ulcerative colitis established.

**Relation to Erythema Nodosum.**—Erythema nodosum occurred in eight patients in the combined series (21 per cent.); other rashes recorded included pyoderma, eczema, urticaria, purpura, psoriasis, ulcerations, and various non-specified "rashes". Seven of the eight patients with erythema nodosum showed joint involvement at that time. In one the arthritis and erythema nodosum occurred with the

Fig. 13.—Case 16, chart showing normal E.S.R. during remission of arthritis.

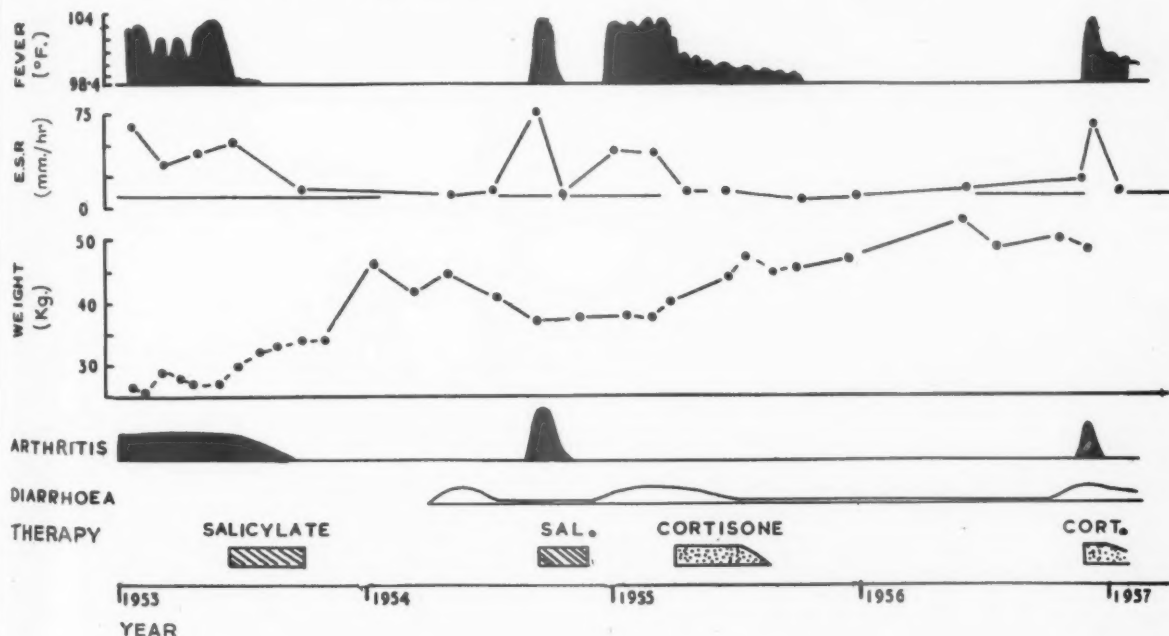




TABLE III  
SYNOVIAL FLUID IN ULCERATIVE COLITIS

Case No.	Protein (g. per cent.)	Relative Viscosity	Cells (c. mm.)		Growth
			Total	Polymorphs (per cent.)	
1	2.0	—	—	—	0
2	2.5	3.3	4,400	75	0
4	2.5	—	12,800	80	—
5	3.1	—	28,000	91	0
14	3.8	4.1	42,400	98	0
15	5.4	4.5	10,000	90	0
16	5.5	7.7	4,000	—	0
Ropes and Bauer (1953) Three to five cases	2.9 to 5.6	8.2 to 13.0	350 to 11,800	0 to 97	0

onset of diarrhoea and settled in a week. In Case 15 (Table II), erythema nodosum developed 3 months after the onset of diarrhoea and on the same day

as pericarditis and polyarthrits, after an attack of episcleritis (Fig. 14). The antistreptolysin titre later became normal. In two cases the erythema nodo-

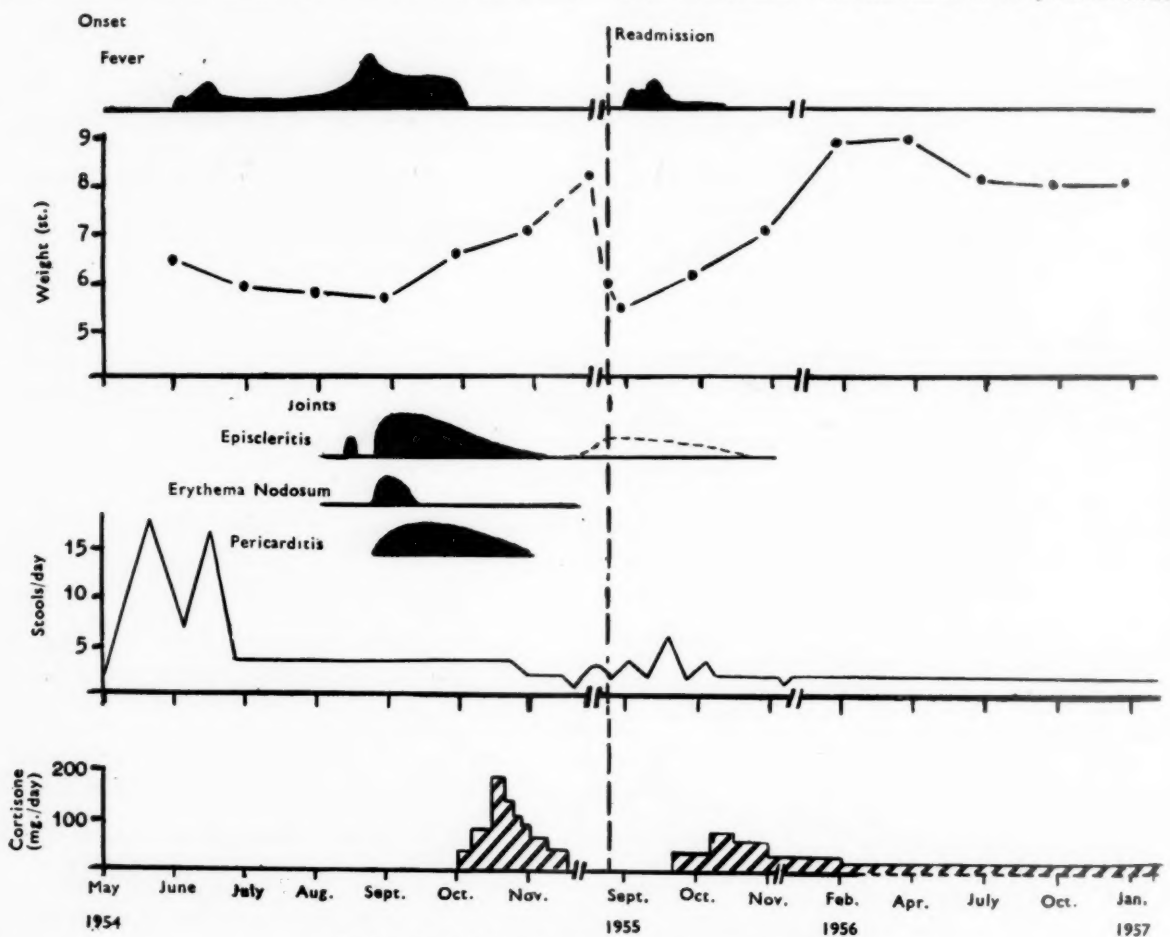


Fig. 14.—Case 15, chart showing response to cortisone therapy.

sum occurred 3 months after the onset of colitis and the arthritis at about the same time. In two cases it occurred with exacerbations of colitis 13 and 16 years after the first onset of symptoms, and was associated with an acute arthritis which settled without residua in a few weeks. In another case with joint involvement, it was present with arthritis 23 years after the onset of colitis. The spots tended to appear on the knees more often than in erythema nodosum without ulcerative colitis, and sometimes as in Case 14 they recurred. The multiple recurrence of erythema nodosum with ulcerative colitis has been noted by Wright and Kenwood (1956) and by Sulzberger (1945); ulceration, as noted by Kelley and Logan (1956), was not seen in this series.

**Relation to Rheumatic Fever.**—This was said to have occurred in five of the 98 Hammersmith and Taplow patients reviewed, including two of those with arthritis (Cases 1 and 14). In three cases this occurred in childhood (at 6, 10, and 30 years before

the onset of ulcerative colitis) and in two others at the age of 24 and 18 years (12 and 7 years before the onset of colitis). In none of these five cases were cardiac residua noted. Although it seems probable that some of these were in fact rheumatic fever attacks, it is also possible that they were prodromal arthritis associated with the gut lesion, since in other patients the joint disease has been so diagnosed (Case 13) before the significance of the occasional loose stool was appreciated. There is a widespread but unfounded belief that a fever which responds to salicylates is rheumatic. The fever of ulcerative colitis responds well to aspirin (Case 16, Fig. 15) and to cortisone (Case 15, Fig. 14) but not to antibiotics.

**Relation to Gut Exacerbations.**—While arthritis may precede obvious diarrhoea, in most instances diarrhoea and arthritis occur together or arthritis follows an exacerbation of gut symptoms. The majority of patients in this series had mild or

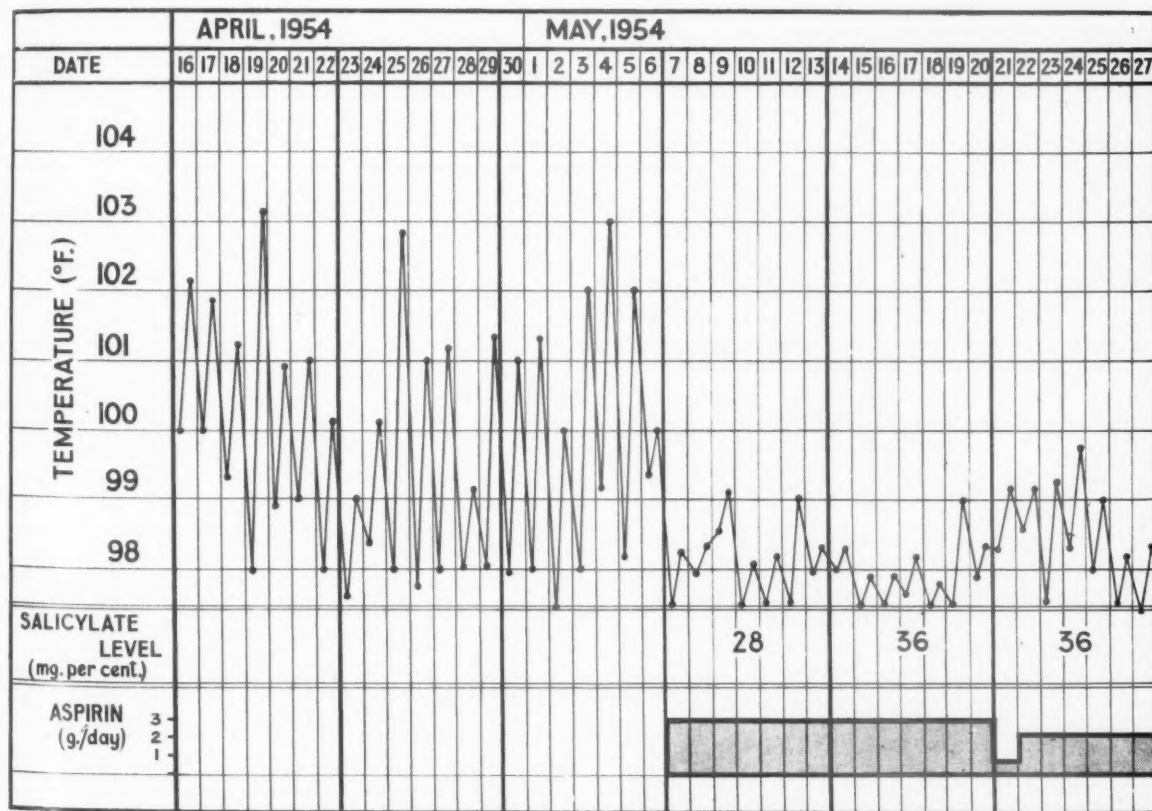


Fig. 15.—Case 16, chart showing response to aspirin therapy.

moderate ulcerative colitis with fairly frequent remissions. It seems probable, however, that the gut lesion may be "active" at a subclinical level and that arthritis, like the skin complications, is always secondary to the intestinal disease. Thus in Case 13, with no bowel complaints and with two normally-formed motions per day, a barium enema disclosed gross colonic disease (Fig. 5, p. 173). In only one case could the ulcerative colitis be regarded as fulminating (Case 30) and this patient developed arthritis 11 months after a sub-total colectomy, at which time she showed a persistently inflamed recto-sigmoid junction.

**Relation to Ileostomy, Colectomy, etc.**—Seven patients had colectomy performed and two a partial colectomy. In other reported series (e.g. Brooke, 1954) colectomy led to remission of joint symptoms in seven out of eight cases. Brooke (1956) noted arthritis in seventeen patients. Of the fourteen who survived the operation, two had an occasional arthralgia, one a brief recurrence, and one no joint remission. Brooke (1954) also noted that arthritis might start after the removal of the colon. Of the patients here reported, one developed severe generalized arthritis for the first time after colectomy, associated with a fistula at the site of the ileostomy; this finally settled down after 3 years, but left residual limitation (Case 3). In another patient the arthritis had settled spontaneously before an ileostomy and total colectomy were successfully performed; since then the patient has had one attack of pain and swelling in an elbow, which subsided leaving limitation of extension of that elbow by 15° but no radiological change. Others have done as well with ileostomy alone.

Arthritis may not appear until as long as 3 years after ileostomy, it may persist for 11 years and yet be cured by colectomy (Campbell, 1938). Bargen, Lindahl, Ashburn, and Pemberton (1943) found that eleven patients with recurrent chronic arthritis after ileostomy did better than five in which the arthritis antedated the operation.

Eight patients received steroid therapy, and in all except one (Case 14) a satisfactory remission of arthritis occurred, although mild bowel symptoms persisted in two. Thus it is suggested that the arthritis is likely to improve if the bowel symptoms improve.

#### Selected Case Reports

**Case 1 (Table II),** a boy aged 16 in 1955, was first seen complaining of pain in the hips, knees, and feet of 6 months' duration. He had had painful knees for 3 months when aged 14, diagnosed as sub-acute rheu-

matism, and at the age of 10 he had had pain and swelling of one knee which persisted for one month and was diagnosed as rheumatic fever.

On examination he showed pain and limitation of both hips, soft tissue swelling, and effusion into both knees, and some tenderness of both heels. There was no limitation of back movement. His general condition was excellent. The erythrocyte sedimentation rate was 61 mm./hr. Plasma: albumin 2.8 per cent., globulin 5.3 per cent. X rays showed complete fusion of both sacro-iliac joints (Fig. 2). The peripheral joints were treated with deep x-ray therapy with good effect, but 7 months later he developed diarrhoea with blood in the stools and marked loss of weight. With this he had a relapse of arthritis affecting the knees, ankles, and heels. On re-admission in January, 1956, he showed effusions and soft tissue swelling into the right knee, soft tissue swelling of the left ankle, and tenderness of both heels.

Positive investigations included erythrocyte sedimentation rate 60 mm./hr, plasma proteins 8.2 g. per cent., albumin 3.3 g. per cent., globulin 4.9 g. per cent., and sigmoidoscopy typical of ulcerative colitis. All other investigations, including those for T.A.B.A. agglutinins, stools, pathogens, L.E. factor, and Rose-Waaler test were negative.

X rays of the knees now showed erosions of both tibial plateaux, and the os calcis shows incomplete erosions beneath the insertion of the Achilles tendon.

As he showed no tendency to improve on a conservative regime, cortisone therapy was commenced in April, 1956. He has continued on this regime until the present (1958) and on 75 mg./day has no residual signs of arthritis and no limitation of back movement and, is in excellent general condition. He is maintaining his weight satisfactorily, but still has slight diarrhoea (two to three motions a day with occasional blood). Sigmoidoscopy is still abnormal and the erythrocyte sedimentation rate is now 3 mm./hr.

**Case 3 (Table II),** a woman aged 38 in August, 1951, was first seen with a history that she had developed ulcerative colitis in November, 1949, which had persisted in a continuously active state until an ileostomy was performed in October, 1950, followed by a complete colectomy in January, 1951. Shortly after this she developed a fistula at the site of the ileostomy, and in May, 1951, she developed a severe generalized acute arthritis, which was still evident on admission.

On examination she showed involvement of the neck, both shoulders, left elbow, both wrists, and second proximal interphalangeal joint of the second right toe, and in addition she had flexor tendon-sheath effusion of the right hand. The erythrocyte sedimentation rate was 120 mm./hr, haemoglobin 13.6 g. per cent., and differential agglutination test negative (1:2). She was treated with a short course of ACTH (for 5 days) and intensive physiotherapy.

The ileostomy was repaired in October and she was finally discharged in December, 1951, much improved, with little residual trouble from the arthritis, apart from limitation of both wrist joints.

She remained well until August, 1953, when she had a recurrence of the fistula at the site of the ileostomy, and this was followed by recurrence of arthritis mainly in the hands, knees, and left foot. This decreased in intensity but she still had some residual swelling with a very painful swollen right wrist when admitted for repair of the fistula in January, 1954. X rays of the wrist showed erosions (Fig. 8). She was again treated with ACTH, and there was an excellent response as regards the joints, and by the time of discharge in April, 1954, her joints had settled to normal, apart from residual limitation of the wrists, and this was the state when she was last seen in November, 1956.

**Case 8 (Table II),** a woman aged 44 when first seen in 1951 had had diarrhoea for 10 years; in the last 6 months it had become worse and was accompanied by acute arthritis of the right foot and left shoulder.

On examination, the left shoulder, both acromioclavicular joints, right ankle, one metatarsophalangeal joint, and one distal interphalangeal joint were involved (Fig. 1a). X rays showed periostitis and erosion (Fig. 1b). The erythrocyte sedimentation rate was 65 mm./hr, differential agglutination test 1 : 4. Sig-moidoscopy and barium enema were positive. The arthritis lasted for 6 months only, but in the last 7 years she has had recurrent mild bouts of diarrhoea with occasional involvement of the shoulder, the left first metacarpophalangeal joint, and the third left distal interphalangeal joint. Now at the age of 51 she shows no clinical residua; the erythrocyte sedimentation rate is 20 mm./hr, and the differential agglutination test 1 : 2, but x rays show a healed erosion in a metatarsal head (Fig. 1c).

**Case 13 (Table II),** a girl aged 14 when first seen in February, 1951, had first developed a flitting arthritis 6 years before at the age of 8; the arthritis was associated with fever and followed by diarrhoea with blood in the stools. This illness, diagnosed as rheumatic fever, had lasted for 3 months. Some 14 months later she had a further bout of arthritis in the knees, again followed by diarrhoea, which persisted for about 6 months. One year later, in October, 1948, she had further poly-arthritis involving elbows, ankles, and knees, followed again by diarrhoea, both remitting after 3 months. She had two further slight flares of knees and ankles in March and October, 1950, associated each time with mild diarrhoea.

In February, 1951, she gave a history of flitting arthralgia for some 3 weeks, persistent pain and swelling in right wrist, and diarrhoea with blood in the stools. At this time the erythrocyte sedimentation rate was 60 mm./hr and the differential agglutination test 1 : 2. A biopsy specimen of the synovial membrane of the right wrist was compatible with rheumatoid arthritis (Fig. 9). She rapidly improved but later in the year developed a brief synovitis of the left ankle not associated with diarrhoea.

She has since taken up an active career of nursing and

her general condition has remained excellent despite a persistently high erythrocyte sedimentation rate. At a follow-up examination in January, 1957, she was found to be in good health, passing two well-formed stools per day but with slight residual limitation of neck and right wrist movement. The back movement was good. The erythrocyte sedimentation rate was 47 mm./hr, and the differential agglutination test again negative. A barium enema, however, showed typical ulcerative colitis affecting the whole colon (Fig. 5). Bilateral sacro-iliitis, erosions of the ischia, and great trochanters (all symptomless), and cystic lesions in the acetabular margins were seen radiologically (Fig. 3). In the neck there was an anterior erosion of the third cervical vertebra of the type described by Romanus (Fig. 4).

**Case 14 (Table II),** a woman aged 42 when first seen in 1948, gave a history that she first developed ulcerative colitis at the age of 19, and that this was followed by arthritis at the age of 24. From then until 1935 she had bouts of colitis associated with flitting arthritis mainly in the knees lasting about 2 months almost every year. Between attacks she was completely well.

6 weeks before her attendance in 1948 she had developed severe colitis, followed 2 weeks later by arthritis of the knees and right wrist and erythema nodosum (Fig. 6). The erythrocyte sedimentation rate was 107 mm./hr, and the radiological appearance of the joints was compatible with rheumatoid arthritis. She slowly improved on a conservative regime, but some 4 months later relapsed again with further arthritis involving the left wrist and shoulders and a recurrence of the rash. Again she improved, only to relapse 3 months later with a severe attack of colitis followed by much more generalized arthritis, now involving the proximal interphalangeal joints of both wrists and shoulders as well as the knees. Since that time she has shown no complete remission of either the colitis or the arthritis, though these have varied from time to time. From August, 1952, she had residual deformities in the proximal interphalangeal joints of all fingers, the third and fourth metacarpophalangeal joints of both hands, wrists, and knees, and the right mid-tarsal joint. The erythrocyte sedimentation rate was 55 mm./hr, and differential agglutination test negative (1 : 2).

She then improved somewhat, clinically, but in 1954 the arthritis again became worse with further involvement of left wrist and right shoulder, large effusions into the knees, and for the first time a skin rash like that seen in Still's disease.

In 1956 she was put on to delta-cortisone with some improvement. When seen in 1957, she had no rash, four to five motions a day, and clinical involvement of the knees, with effusion of the right elbow, left ankle, wrists, metacarpophalangeal second and third right and left, proximal interphalangeal third left, and second left proximal interphalangeal toe joint. The erythrocyte sedimentation rate was 60 mm./hr, and differential agglutination test 1 : 2. X rays showed erosions of numerous joints and obliterative erosion and sclerosis of the sacro-iliac joint.



**Case 16, a boy aged 12** when admitted to another hospital in December, 1951, with a 3-month history of weight loss, abdominal pain, and vomiting, was thought to be suffering from *tabes mesenterica* and was treated with streptomycin and P.A.S. Shortly after admission he developed bilateral knee effusions which were treated with salicylates with improvement. He was discharged 6 months later but re-admitted after 3 months for removal of an "acute appendix": at this time no glands were found in the abdomen. He developed a wound abscess and this was followed by development of an abdominal sinus. He again had troublesome knee effusions, and a biopsy was taken of one knee (Fig. 12). He was transferred to Taplow in January, 1953, as a case of Still's disease with pain and swelling of the knees, together with persistent colic and a discharging abdominal sinus. There were bilateral joint effusions but no other abnormality. A barium meal and fat balance were normal. The erythrocyte sedimentation rate was raised and he ran an intermittent fever. Differential agglutination test 1:1. The joint fluid contained 4,000 cells/c.mm., relative viscosity 7.7, protein 5.5 g. per cent., culture negative.

In view of the persistent sinus and colic the fistula leading to the appendicular stump was excised in April, 1953. However, post-operatively his pyrexia and arthritis persisted. He was treated with salicylates with some improvement (Fig. 15).

In April, 1954, he had a short bout of diarrhoea and was re-admitted for one month in August, 1954, because of recurrence of arthritis involving the elbows, knees, wrists and ankles. At this time he was pyrexial, erythrocyte sedimentation rate 45 mm./hr, differential agglutination test 1:2. He rapidly improved on salicylates.

He was re-admitted in February, 1955, with diarrhoea, severe for one month and probably mild for three previous months. Sigmoidoscopy was negative but a barium enema showed ulceration and polypi in the transverse and descending colon. He was treated with sulphasuxidine and a short course of cortisone with a satisfactory response, and was finally discharged on June 24, 1955.

He remained well until later in 1956 when he developed a mild temporary exacerbation of arthritis involving both knees and right elbow, together with marked loss of weight. Differential agglutination test 1:8. No x-ray or clinical joint residua. No sacro-iliac change.

### Discussion

The most interesting feature of this syndrome is its relationship to rheumatoid arthritis, Reiter's disease, and ankylosing spondylitis. Since in all cases except two, the course of the joint lesions was very different from that of rheumatoid arthritis and the Rose test was usually negative, these cases can hardly represent the purely coincidental association of the two diseases. If, however, this syndrome is, *e.g.* rheumatoid arthritis precipitated by colitis, the colitis or colitic diathesis must modify the rheumatoid arthritis considerably to produce the differences noted above.

Both Reiter's syndrome and ankylosing spondylitis occur predominantly in males, whereas only two of our six cases with sacro-iliac involvement were males. Episcleritis and iritis were seen only once, and balanitis, keratoderma, urethritis, and aortitis not at all. It seems most probable that this is a separate disease of the joints of a somewhat similar nature to those noted above, caused by the same factors as those that produce the disease of the gut or perhaps secondary to gut disease. Disease of the gut may produce a secondary arthritis, but this is unlikely because, apart from the dubious joint troubles of Whipple's syndrome and the acute rheumatic fever-like sequelae of dysentery, gut inflammation does not produce secondary arthritis with any noticeable frequency. The clear association in some instances with erythema nodosum, and particularly the acute arthritis occurring only with this in some cases, suggests an "allergic" basis, *i.e.* the active participation of an antibody-forming mechanism.

### Summary

(1) 37 patients suffering from both arthritis and colitis have been reviewed, thirty of whom were seen personally.

(2) In the majority, the colitis was of mild to moderate severity. The arthritis tended to be a recurrent mild and often migratory synovitis, localizing in one or two of the joints longest affected, and frequently remitting. Only rarely did a severe generalized form of arthritis occur.

(3) Nodule formation with a persistently positive differential agglutination titre was seen in only two cases.

(4) Radiological changes did not differ from those seen in rheumatoid arthritis, although healing tended to occur more frequently and there was a moderately high incidence of sacro-iliac involvement.

(5) In view of the nature of the arthritis together with the negative differential agglutination test usually found, it is concluded that a separate form of arthritis is associated with the ulcerative colitis; it is similar to that occurring acutely in erythema nodosum due to other causes, but it may last longer and may recur; in such cases chronic residual changes closely resembling those of rheumatoid arthritis may be seen.

We wish to thank our colleagues at the Postgraduate Medical School, London, and the Canadian Red Cross Hospital, Taplow, particularly Dr. Sheila Sherlock and Dr. George Hadley, who allowed us to use data from their cases and also referred cases to us; also Mr. G. P. Arden who kindly performed the biopsies for us.

We are very grateful to Dr. N. F. Coghill of the West Middlesex Hospital and Dr. G. Kellock of the Central Middlesex Hospital, who in addition to reviewing their cases of ulcerative colitis at our request, very kindly arranged for us to see particular cases and obtain blood samples and x rays, and allowed us to use these data.

We should also like to thank Dr. Francis Scott for the frequent repetitions of the differential agglutination test examinations which he undertook.

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## Arthrite associée à la colite ulcéreuse

## RÉSUMÉ

(1) On a re-examiné 37 malades, dont 30 personnellement, tous atteints d'arthrite et de colite ulcéreuse.

(2) Chez la plupart d'entre eux, la colite était bénigne ou modérée. L'arthrite tendait à présenter la forme de synovite bénigne, récurrente et souvent migrante, souvent localisée dans une ou deux des articulations atteintes le plus longtemps, avec de fréquentes remissions. La forme sévère d'arthrite généralisée n'apparaissait que rarement.

(3) La formation de nodules avec la réaction d'agglutination différentielle toujours positive n'a été observée que dans deux cas.

(4) L'image radiologique n'était pas différent de celui observé dans l'arthrite rhumatismale, bien que la guérison tendait à se produire plus souvent et l'implication sacro-iliaque était assez fréquente.

(5) En vue de la nature de l'arthrite, ainsi que de la réaction d'agglutination différentielle habituellement négative, on conclut que cette arthrite, associée à la colite ulcéreuse, représente une forme à part; elle ressemble au type aigu survenant au cours de l'érythème noueux du aux autres causes, mais peut durer plus longtemps et peut récidiver; dans ces cas on peut observer des altérations chroniques résiduelles se paraissant beaucoup à celles de l'arthrite rhumatismale.

## Artritis asociada a la colitis ulcerativa

## SUMARIO

(1) Se revistaron 37 enfermos con artritis y colitis ulcerativa; 30 de ellos fueron examinados personalmente.

(2) En la mayoría de ellos, la colitis fué benigna o moderada. La artritis tendía a presentar la forma de sinovitis benigna, recurrente y, a menudo, migrante, frecuentemente en una o dos articulaciones afectas desde mucho tiempo, con remisiones frecuentes. La forma de poliartritis generalizada severa fué muy rara.

(3) La formación de nódulos con una reacción de aglutinación diferencial siempre positiva fué observada tan sólo en dos casos.

(4) Las alteraciones radiológicas no fueron diferentes de las observadas en la artritis reumatoide, pero curas tendían a producirse más a menudo y la implicación sacro-iliaca fué frecuente.

(5) En vista de la naturaleza de la artritis, así como de la reacción de aglutinación diferencial generalmente negativa, se concluye que esta artritis, asociada a la colitis ulcerativa, es una forma aparte; esta forma se parece al tipo agudo que ocurre en el eritema nodoso debido a otras causas, pero puede durar más tiempo y puede reincidir; en tales casos se pueden ver alteraciones crónicas residuales muy parecidas a las de la artritis reumatoide.

## EFFECT OF LONG-TERM TREATMENT WITH CORTICOSTEROIDS ON ADRENOCORTICAL FUNCTION\*

### STUDIES IN RHEUMATOID ARTHRITIS IN THE LIGHT OF THE RESPONSE OF PLASMA-FREE AND TOTAL 17,21-DIHYDROXY-20-KETOSTEROIDS TO INTRAVENOUS CORTICOTROPIN

BY

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It is well known that prolonged treatment with corticosteroids interferes with normal adrenocortical function, causing involvement or atrophy of the gland. This was first demonstrated in animals by Ingle and Kendall (1937) with adrenocortical extracts. Since the introduction of cortisone in clinical medicine, a great deal of evidence has accumulated concerning adrenocortical hypofunction or atrophy after the administration of this agent (e.g. Sprague, Power, Mason, and six others, 1950; O'Donnell, Fajans, and Weinbaum, 1951). These effects are assumed to be due to suppression of the release of ACTH from the adenohypophysis.

The degree and duration of adrenocortical hypofunction produced by the administration of corticosteroids has considerable clinical significance. Certain aspects of the problem have been discussed in earlier studies (Engleman, Krupp, Johnson, Welsh, Wrenn, and King, 1953; Fredell, Johnson, Krupp, Engleman, and McGrath, 1955; Hansen, Fischer, and Bræchner-Mortensen, 1955; Christy, Wallace, and Jailer, 1956; Larzelere, Barthold, Willett, Feichtmeir, Wilson, and Engleman, 1957).

The purpose of the investigation now reported was to determine the adrenocortical function in a group of patients with rheumatoid arthritis after prolonged treatment with corticosteroids, and to follow up the restoration of function after the withdrawal of therapy. The ability of intramuscular ACTH administration to promote the normalization of adrenocortical function was also studied.

#### Material and Methods

The series comprised ten patients, nine of whom suffered from rheumatoid arthritis. The diagnosis in

Case 2 (Table I) was not confirmed, but a collagen disease, related to rheumatoid arthritis, was suggested. In one case with rheumatoid arthritis there was a positive L.E.-test indicating the presence of disseminated lupus erythematosus (Case 7, Table II). All the patients were hospitalized during the study. The duration of prolonged continuous therapy with corticosteroids (cortisone, hydrocortisone, or prednisone) varied from 3 months to 6 years (average 2 years 8 months). In most patients treatment had been started with cortisone or hydrocortisone, which was later on replaced by prednisone when this drug became available. Only one patient was still receiving hydrocortisone at the time of the investigation. The dosage of steroids was in most cases small or moderate (prednisone 5-20 mg. per day). In some cases, however, the dosage of steroids had previously been somewhat higher.

The response of plasma 17,21-dihydroxy-20-ketosteroids (17-OH-CS) to intravenous ACTH drip infusion was used as an index of adrenocortical function or capacity. All drug therapy was stopped one day before the first test. The experiment started at 7.30 to 8.30 a.m., after about 14 hrs' fast. The blood samples were drawn from the cubital vein immediately before the administration of ACTH and 2 and 6 hrs later. The ACTH (ACTHAR, Armour Laboratories, or Cortrophine, Organon) was given by continuous drip infusion in 0.9 per cent. saline or 5 per cent. glucose solution. The dosage was 12-18 I.U. ACTH in 600 to 900 ml. solution over 6 hrs.

Both free and total plasma 17-OH-CS (free + glucuronides) were assayed in most instances. The method of Silber and Porter (1954), as modified by Peterson, Wyngaarden, Guerra, Brodie, and Bunim (1955) and Peterson, Karrer, and Guerra (1957), was used for the determination of free plasma 17-OH-CS. The total plasma 17-OH-CS was assayed by the procedure developed by Krusius and Oka (1958). For this purpose 400 units bacterial  $\beta$ -glucuronidase (Sigma) were dissolved in 1 ml. redistilled water and pipetted to 0.5 ml. 1 M potassium dihydrophosphate ( $\text{KH}_2\text{PO}_4$ ), 0.3 ml. 5 per cent. sodium bisulphite ( $\text{NaHSO}_3$ ), and 5 ml.

\* The subject of this study was proposed to us by Dr. Currier McEwen, New York University, Bellevue Medical Center, and this material was presented in part at the International Congress on Clinical Chemistry at Stockholm on August 22, 1957.



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TABLE I

RESPONSE OF PLASMA 17-OH-CS TO INTRAVENOUS ACTH IN FIVE PATIENTS WITH RHEUMATOID ARTHRITIS AFTER PROLONGED TREATMENT WITH CORTICOSTEROIDS. ALL DRUG THERAPY WAS STOPPED

Case No.	Sex	Age (yrs)	Duration of Steroid Therapy (yrs)	Last Steroid Administered	Dose per Day (mg.)	Time since Withdrawal of Steroids (days)	Free/Total Plasma 17-OH-CS ( $\mu$ g. per cent.) after		
							0 hr	2 hrs	6 hrs
1	M	40	5	Prednisone	12.5	1	23/	27/	28/
						14	25/	29/	34/
						30	18/35	29/48	42/67
2	M	38	4	Prednisone	10	1	15/	18/	22/
						12	7/	22/	29/
3	F	56	3	Prednisone	5	1	9/16	19/25	19/34
						9	10/	22/	31/
4	F	49	1	Prednisone	10	1	22/34	32/54	35/65
						8	17/33	36/	44/76
5	F	17	2	Prednisone	20-7.5	1	0/8	4/15	9/12
						8	14/22	23/34	27/41
						30	17/27	27/48	34/59

TABLE II

RESPONSE OF PLASMA 17-OH-CS TO INTRAVENOUS ACTH IN FIVE PATIENTS WITH RHEUMATOID ARTHRITIS AFTER PROLONGED TREATMENT WITH CORTICOSTEROIDS  
Cortrophine-Z 20 I.U. twice daily was administered intramuscularly after the first test

Case No.	Sex	Age (yrs)	Duration of Steroid Therapy (yrs)	Last Steroid Administered	Dose per Day (mg.)	Time since Withdrawal of Steroids (days)	Free/Total Plasma 17-OH-CS ( $\mu$ g. per cent.) after		
							0 hr	2 hrs	6 hrs
6	F	46	6	Hydrocortisone	40	1	15/29	23/35	23/33
						9	16/19	65/71	77/92
7	F	67	3½	Prednisone	10	1	17/25	20/34	26/38
						7	11/27	29/68	44/85
8	F	49	2½	Prednisone	7.5	1	23/32	24/34	23/33
						8	11/17	35/54	41/71
9	F	50	½	Prednisone	12.5	1	5/	10/34	10/40
						8	46/80	42/95	53/104
10	F	49	½	Prednisone	50-20	1	4/9	11/16	15/26
						8	14/	37/	53/97

plasma. The mixture, the pH of which was 6.0 to 6.2, was incubated for 48 hrs at 37° C. The addition of sodium bisulphite was made in order to eliminate any interfering chromogens formed in the presence of glucose during the hydrolysis procedure (Louis, Eiler, Streeten, and Conn, 1956).

The adrenocortical capacity was re-estimated in all cases 7 to 14 days after the withdrawal of steroid therapy. A third test was performed in Cases 1 and 5 (Table I) 30 days after the interruption of the treatment with steroids. Cases 1 to 5 were kept without hormone

therapy between the repeated tests (Table I). The other group of five patients (Cases 6 to 10, Table II) received repository intramuscular ACTH injections (Cortrophine-Z, Organon, 20 I.U. twice daily) during the interval between the first and second tests. The plasma 17-OH-CS after 3 days of intramuscular ACTH administration in Cases 6 to 10 was also assayed (Table III, overleaf).

The range of free plasma 17-OH-CS values after 6 hrs' intravenous ACTH infusion in this laboratory was 37 to 46  $\mu$ g. per cent. (mean 41  $\mu$ g. per cent.) in cases



TABLE III

PLASMA 17-OH-CS LEVELS IN FIVE PATIENTS WITH RHEUMATOID ARTHRITIS 4 DAYS AFTER THE DISCONTINUANCE OF PROLONGED CORTICOSTEROID TREATMENT, AND AFTER 3 DAYS' STIMULATION WITH INTRAMUSCULAR ACTH INJECTIONS (CORTROPHINE-Z 20 I.U. TWICE DAILY)

Case No.	Free/Total Plasma 17-OH-CS ( $\mu$ g. per cent.)
6	49/70
7	18/55
8	27/49
9	37/81
10	37/90
Mean	34/69

without demonstrable disturbances of adrenocortical function (Krusius, Oka, and Kärkelä, 1958).

### Results

The results are presented in Tables I to IV and in the Figure. An impaired adrenocortical response to ACTH was recorded in all cases one day after the withdrawal of steroid therapy. In Case 4, however, the response of plasma 17-OH-CS to ACTH was very near the normal range, despite one year's treatment with 10 mg. prednisone daily. The lowest plasma 17-OH-CS values after 6 hrs' ACTH infusion were obtained in cases which had received a moderate or high dosage of prednisone (Cases 5, 9, and 10). The duration of corticoid treatment seemed to be of less importance, because these cases had been treated for shorter periods than the others. The average plasma 17-OH-CS values in the first adrenocortical capacity test were, in all ten cases, 13.3  $\mu$ g. per cent. before ACTH, 18.8  $\mu$ g. per cent. after 2 hrs, and 21  $\mu$ g. per cent. after 6 hrs of ACTH infusion.

In the group of five patients kept without any medication between the first and second (or third) capacity test (Table I) there was a slight but distinct improvement of adrenocortical response 8 to 14 days after the withdrawal of prednisone, but a normal capacity test was obtained only in Case 4. In two cases the test carried out after 30 days without steroid treatment showed a further improvement of adrenocortical response, the result was entirely normal in only one of them. In none of these patients could any distinct clinical signs of adrenocortical insufficiency be observed.

In all five cases in which intramuscular ACTH injections were given between the first and second test, a normal or raised adrenocortical response was observed 7 to 9 days after the withdrawal of steroid therapy. This was reflected in both the

plasma-free and total 17-OH-CS levels. The restoration of the adrenocortical response in this group was very quick, as is shown by the plasma 17-OH-CS levels measured after not more than 3 days of intramuscular repository ACTH administration (Table III). Three of these values were above the lower limit of normal.

The degree and rate of restoration of the adrenocortical capacity differed greatly both in individual cases and in the average estimates in the two groups separately (Figure, opposite).

Roughly the same changes as in the plasma free 17-OH-CS levels were observed in the plasma total 17-OH-CS levels. The ratio of free to total 17-OH-CS varied only slightly both before the tests and after 2 or 6 hrs of ACTH infusion. Nor did the degree of the adrenocortical response to ACTH have any significant influence on the proportion of free to total 17-OH-CS levels, the ratio being about the same in the first as in the second or third capacity tests (Table IV).

TABLE IV

RATIO OF FREE/TOTAL PLASMA 17-OH-CS

Table	Test	Free/Total 17-OH-CS		
		After 0 hr	After 2 hrs	After 6 hrs
I+II	1	0.59	0.58	0.57
I	2-3	0.57	0.61	0.60
II	2	0.59	0.59	0.60

### Discussion

The results indicate that, even after many years of steroid administration, the adrenal cortex responds to stimulation with ACTH, though the response is greatly impaired. The lowest plasma 17-OH-CS values after intravenous ACTH administration were obtained in cases in which the highest prednisone doses had been given. On the other hand, the period of treatment was shorter in these cases than in the rest, suggesting that the decrease of adrenocortical response to ACTH may be more closely related to the size of the steroid dosage than to the duration of the treatment. Individual variations in the degree of adrenocortical hypofunction after long-term steroid treatment are, however, remarkable.

The adrenocortical response seemed to be restored in a few weeks without any treatment, but administration of ACTH accelerates the recovery of the adrenocortical response as measured by plasma 17-OH-CS assays. Thus our results do not entirely support earlier reports, according to which adrenocortical hypofunction may persist for several months after withdrawal of hormone treatment

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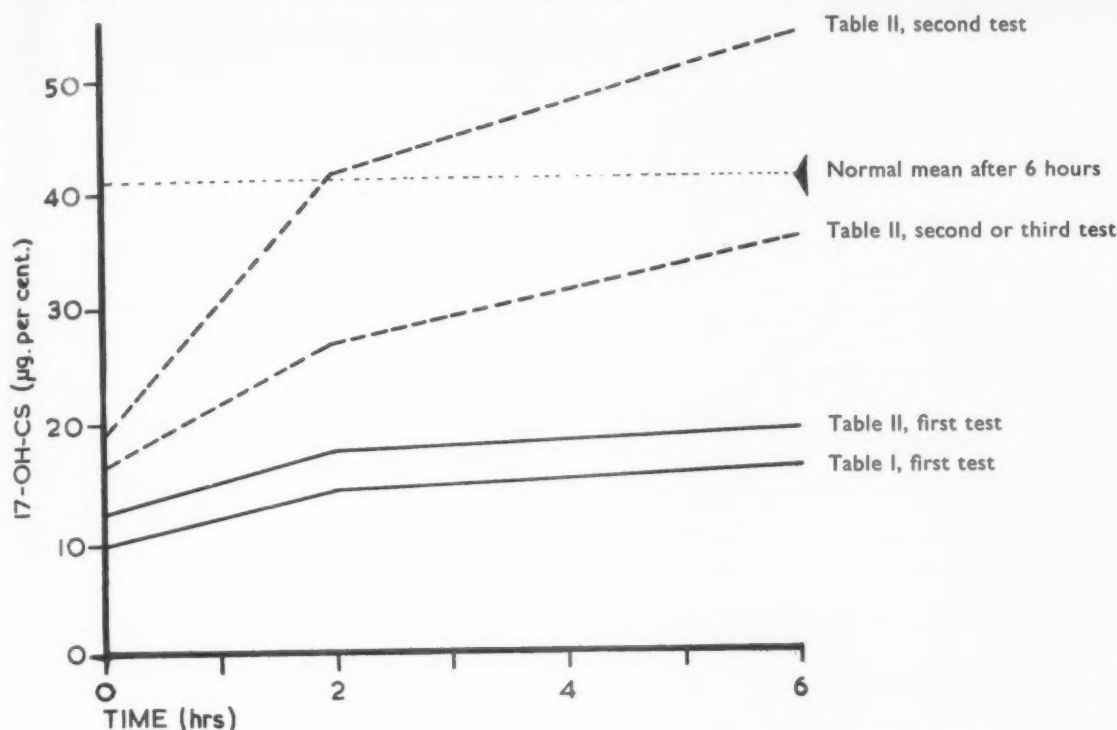


Figure.—Mean curve of adrenocortical capacity tests of the ten patients listed in Tables I and II.

Response of plasma free 17-OH-CS to Intravenous ACTH.

— = First test, performed one day after withdrawal of steroid therapy.  
 - - - - = Second or third test, performed 8 to 30 days later.

(Sprague and others, 1950; Fraser, Preuss, and Bigford, 1952; Salassa, Bennett, Keating, and Sprague, 1953; Bennett, 1954).

On the other hand, our results do confirm the clinical observation that it is useful to give ACTH for some days to patients who have been treated for a long time with steroid hormones in order to accelerate the improvement of adrenocortical function. As this improvement is achieved relatively quickly by ACTH administration after the withdrawal of steroid therapy, there seem to be no real indication for simultaneous treatment with steroids and ACTH, as has been suggested (Vasama, Kalliomäki, Vasama, Näättänen, 1957; Young, De Filippis, Meyer, and Wolfson, 1957).

Our study also shows that the determination of the total 17-OH-CS (free and glucuronidates) in plasma offers no advantages over the determination of free plasma 17-OH-CS, at least in patients with rheumatoid arthritis. The ratio of plasma-free to total 17-OH-CS was constant in all cases, indicating that the conjugation mechanism of 17-OH-CS is not significantly changed either by prolonged steroid therapy or by short-term ACTH administration in patients with rheumatoid arthritis.

#### Summary

The adrenocortical capacity has been studied in ten patients with rheumatoid arthritis after long-term steroid administration, by measuring the response of plasma-free and total 17-OH-CS to intravenous ACTH infusion. An impaired adrenocortical response was recorded in all these cases one day after the withdrawal of the steroid treatment.

The test was repeated once or twice after an interval of 7 to 30 days in order to investigate the time needed for recovery, after which the capacity test would give a normal result. In five patients who received no further treatment, there was a slight but distinct improvement in the adrenocortical capacity 8 to 14 days after the withdrawal of steroid therapy, but a normal response was obtained in only one case. In two of these cases there was a further improvement of the plasma 17-OH-CS response to ACTH stimulation after 30 days, but in only one was the result quite normal.

The remaining five patients were treated by intramuscular repository ACTH injections between the first and second test in order to hasten the restoration of normal function. In all five a normal or hypernormal adrenocortical capacity was observed

7 to 9 days after the withdrawal of steroid therapy. Even after 3 days of ACTH injections the plasma 17-OH-CS level was above the lower limit of normal in three cases out of five.

The ratio of free to total plasma 17-OH-CS varied only slightly in all cases and in all assays performed, indicating that the conjugation mechanism of 17-OH-CS in rheumatoid arthritis is not significantly altered by prolonged corticosteroid or short-term ACTH therapy.

The ACTH preparations used were generously supplied by the Armour and Organon Companies.

The writers are pleased to acknowledge the technical assistance of Miss Elli Sahanen.

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#### Effet du traitement prolongé par des corticostéroïdes sur la fonction surrénocorticale

Etudes de l'arthrite rhumatoïdale à la lumière de la réponse des 17,21-dihydroxy-20-cétostéroïdes plasmatiques, libres et totaux à la corticotropine intraveineuse

#### RÉSUMÉ

On a étudié la capacité surrénocorticale chez dix malades atteints d'arthrite rhumatoïdale après l'administration prolongée de stéroïdes, en mesurant la réponse des 17-OH-CS à l'infusion intraveineuse d'ACTH. Une réponse surrénocorticale affaiblie a été enregistrée dans tous les cas un jour après l'interruption du traitement stéroïde.

Cette épreuve fut répétée une ou deux fois après un intervalle de 7 à 30 jours, pour déterminer le temps nécessaire pour obtenir un résultat normal, signifiant le rétablissement de la fonction. Chez cinq malades, il y eut une amélioration légère mais définie de la capacité

surrénocorticale au bout de 8 à 14 jours après l'interruption du traitement stéroïde, mais une réponse normale ne fut obtenue que dans un seul cas. Dans deux de ces cas il se produisit une amélioration ultérieure de la réponse des 17-OH-CS plasmatiques à la stimulation par l'ACTH au bout de 30 jours, mais le résultat tout à fait normal ne fut observé que chez l'un d'entre eux.

Les cinq malades restants furent traités par des dépôts intramusculaires d'ACTH entre le premier et le second test afin d'accélérer le rétablissement de la fonction normale. Dans tous les cinq cas la fonction surrénocorticale devint normale ou supérieure 7 à 9 jours après l'interruption du traitement stéroïde. Déjà 3 jours après l'injection d'ACTH le taux plasmatique des 17-OH-CS franchit la limite inférieure des chiffres normaux dans trois cas sur cinq.

Le rapport entre les 17-OH-CS plasmatiques libres et totaux ne variait que très peu dans tous les cas et dans toutes les épreuves effectuées, montrant que le mécanisme de conjugaison des 17-OH-CS dans l'arthrite rhumatoïdale n'est pas appréciablement altéré par un traitement corticostéroïde prolongé ou par une brève administration d'ACTH.

#### Efecto del tratamiento prolongado con corticoesteroides sobre la función suprarrenocortical

Investigación de la artritis reumatoide a la luz de la respuesta de los 17,21-dihidroxi-20-cetoesteroides plasmáticos, libres y totales, a la corticotropina intravenosa

#### SUMARIO

Se estudió la función suprarrenocortical en diez enfermos con artritis reumatoide después de la administración prolongada de esteroides, midiendo la respuesta de los 17-OH-CS a la infusión endovenosa de ACTH. Una respuesta suprarrenocortical débil fue notada en todos los casos un día después de haber cesado el tratamiento esteroide.

El experimento fue repetido una o dos veces, entre 7 y 30 días después, para determinar el tiempo necesario para obtener un resultado normal, indicando el restablecimiento de la función. En cinco enfermos hubo una mejoría ligera pero distinta de la función suprarrenal al cabo de 8 a 14 días después de la interrupción del tratamiento esteroide, pero tan sólo en uno la respuesta fue normal. En dos de estos casos la respuesta favorable de los 17-OH-CS plasmáticos a la estimulación por el ACTH fue más pronunciada al cabo de 30 días, pero solamente uno de ellos dió un resultado perfectamente normal.

Los demás cinco enfermos fueron tratados con inyecciones de depósito intramuscular de ACTH entre el primer y el segundo test, con el fin de acelerar el restablecimiento de la función normal. En los cinco casos la función suprarrenocortical llegó a ser normal o superior de siete a nueve días después de la interrupción del tratamiento esteroide. Aun tres días después de la inyección de ACTH la cifra plasmática de los 17-OH-CS rebasó el límite inferior de lo normal en tres de los cinco casos.

Poquísimas variaciones fueron notadas entre los 17-OH-CS plasmáticos libres y totales en todos los casos y en todas las investigaciones, indicando que el mecanismo de conjugación de los 17-OH-CS en la artritis reumatoide no se ve apreciadamente modificado por el tratamiento corticoesteroide prolongado o por una breve administración de ACTH.



# RADOSODIUM CLEARANCE FROM THE KNEE JOINT IN RHEUMATOID ARTHRITIS

BY

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The rate of removal of radioactive sodium from a tissue has been shown by Kety (1949) to be a quantitative measure of the local circulation. This technique has been used extensively to study circulation in skin, subcutaneous tissue, and muscle (McGirr, 1952), and it has been applied to the study of the normal human knee joint (Jacox, Johnson, and Koontz, 1952; Harris and Millard, 1956). In our previous study, simple exponential curves were consistently found. When the counting rate was plotted semi-logarithmically against time, straight lines were obtained for periods up to 60 minutes (Fig. 1). For a series of 23 normal knees, the clearance constant ranged between 0.025-0.080, with a mean value of 0.050 (S.D. 0.021). The effects of manœuvres likely to affect circulation in the joint (arterial and venous occlusion, deep heating with diathermy, and exercise) were studied. In ten subjects the measurement was repeated at an interval varying from 1 to 14 weeks, and these findings showed a close comparison in distribution values for the two groups, although individual knees showed a difference of as much as 100 per cent. on different occasions. The groups had similar mean values (0.050; S.D. 0.017; 0.054; S.D. 0.019). From this experiment it was concluded that the method could be used usefully in studying circulation in the knee joint, and that in the normal knee the results are reasonably reliable and reproducible.

We have now applied the technique to the study of the knee joint in patients suffering from rheumatoid arthritis, by which we mean polyarthritis affecting three or more joints for at least 3 months without other discernible cause.

### Method

The subjects were all in-patients in the rehabilitation unit, with an age range of 20 to 68 years.

The degree of disease activity in the knee joint was graded on a clinical assessment, from 0-3, as follows:

0 = No involvement.

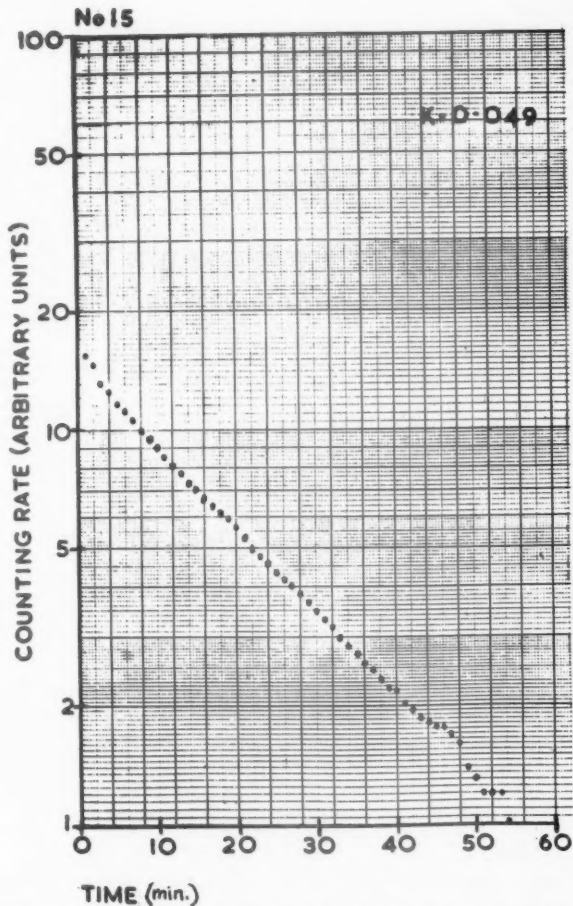


Fig. 1.—Clearance curve from the knee joint of a normal subject showing a straight line for over 50 min.

- 1 = Minor involvement (Tenderness +; pain on use ±; thickening ±; effusion ±).
- 2 = Moderate involvement (Heat +; tenderness +; or ++; pain at rest ±; pain on use + or ++; thickening +; effusion -, +, or ++).
- 3 = Severe involvement (Heat +; tenderness ++; pain at rest +, or ++; pain on use + or ++; thickening +; effusion + or ++).



The degree of effusion present was also graded 0-3, as follows (modified from Millard and Parry, 1953):

- 0 = No effusion or thickening.
- 1 = Just perceptible trace of fluid; or thickening.
- 2 = Clearly visible effusion.
- 3 = Moderate or large effusion.

The erythrocyte sedimentation rate (Westergren) was also noted.

The subject rested on a couch for 30 minutes with the legs horizontal, comfortably supported in plaster back splints. The room temperature remained constant during each observation, but varied on different days between 19-22° C. Between 0.2-0.5 ml. isotonic saline, containing 5-10 microcuries <sup>24</sup>Na was injected rapidly into the knee joint through a 2-in. long, 26-gauge hypodermic needle, with the usual aseptic precautions. The approach was retropatellar, from behind the medial border. No local anaesthetic was used. In the presence of an effusion the injection was technically very simple. No pain was experienced and in only two out of about 100 injections was it considered that the injection had not been placed intra-articularly. Fluid was not aspirated. Two unshielded scintillation counters were arranged at either side of the knee joint, to give a wide-field view of the joint. Each was connected to a rate-meter. The initial counting rate was about 1,000 per second. The counting rate of each counter was recorded at minute intervals to background level. The sum of each pair of readings, less the background count, was plotted semi-logarithmically against time. The purpose of the double counting system was to compensate for any movement of the joint or sodium shift within the joint, and the composite count gave a smoother curve than either of its components (Harris and Millard, 1956). This plot gives a fairly straight line. From the graph, the clearance constant, K, was found where

$$K = \frac{\log C_1 - \log C_2}{0.4343 (t_1 - t_2)}, \text{ where } C_1 \text{ and } C_2 \text{ are counting}$$

rates at times  $t_1$  and  $t_2$  respectively.

In addition to single clearance studies, the sodium clearance measurements were repeated after an interval in some knees, and also at a certain interval after intra-articular hydrocortisone injections.

### Results

Radiosodium clearance measurements were made on 69 different knees. This includes five pairs of

knees which were studied simultaneously by a single-counter technique. In 63 of the 69, a good single straight line was found. The six others showed a more complex curve which consisted of two dissimilar gradients. In five of the six, the gradient of the curve suddenly slowed between 14 to 22 minutes after injection, by about 50 per cent. The sixth subject showed a double curve with an increase in gradient of nearly 100 per cent. at 16 minutes. There was no obvious correlation of the double curve with either local disease activity or the grade of effusion present. (The initial portion of the curve has been used in calculating the clearance constant in these subjects.) We have not seen this complex curve in over 100 observations in a control group of fifty subjects who were either normal or suffering from a variety of non-rheumatoid diseases (ankylosing spondylitis, osteo-arthritis, neuropathic joints).

The clearance constant for the whole group varied considerably with a range between 0.020 and 0.191 (mean value 0.070, S.D. 0.040). This is much beyond the range for the normal non-arthritic knee.

**Correlation with Local Disease Activity.**—Table I shows clearly a close relation between the clearance rate and the degree of local activity of the disease—the more active the knee the higher the clearance rate of the group. However, individual knees may not show this and five out of the twelve knees graded as “severely involved” had values within the normal range. On the other hand no knees in rheumatoid subjects had abnormal values at Grades 0 and 1 (*i.e.* without clinical signs, or with only minor involvement). In Grade 2, 33 per cent. had clearance values higher than the range found in normal knee joints. These findings are brought out more clearly in Fig. 2 (opposite), which also includes the findings for fifty normal knees, from a control group of “non-rheumatic” subjects.

**Correlation with Effusion.**—By definition of our method of assessment, no subject with Grade 0 activity had an effusion, and all subjects with Grade 3 activity had effusions. Thus the likelihood of an effusion being present increased with the local

TABLE I  
CLEARANCE VALUES OF NORMAL AND RHEUMATOID KNEE JOINTS  
(GRADED 0-3 ACCORDING TO LOCAL DISEASE ACTIVITY)

State of Knee ..	Normal Controls	0	1	2	3
No. of Subjects ..	50	19	11	27	12
Range .. .. .	0.02-0.090	0.02-0.093	0.032-0.090	0.025-0.178	0.048-0.191
Mean .. .. .	0.051	0.050	0.057	0.074	0.106

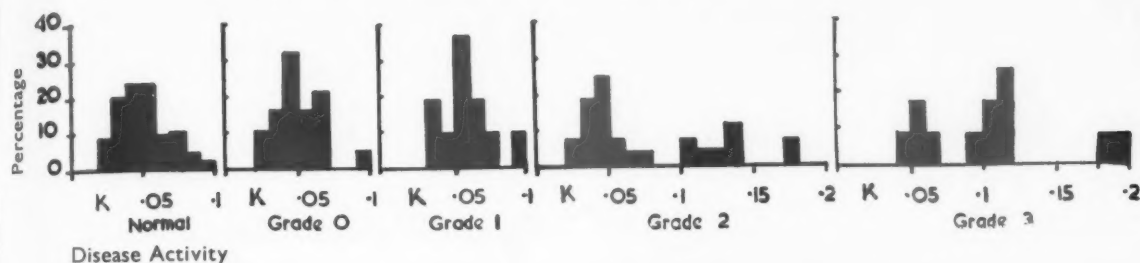


Fig. 2.—Clearance constants (K) of rheumatoid knee joints graded according to local disease activity.

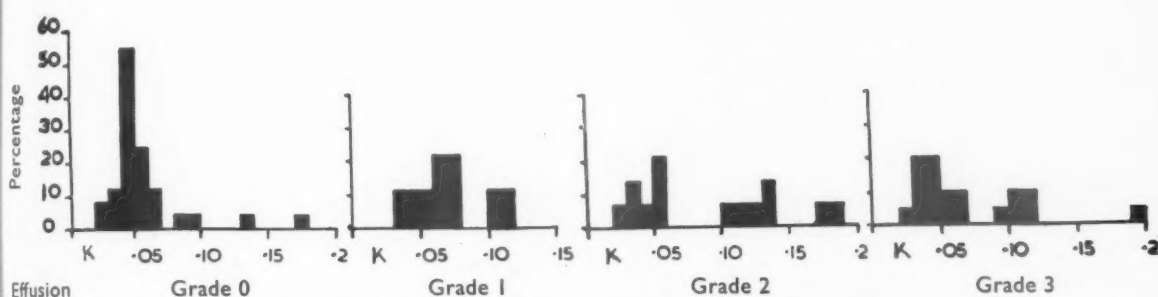


Fig. 3.—Clearance constants (K) of rheumatoid knee joints graded according to size of effusion.

TABLE II

CORRELATION OF CLEARANCE CONSTANT, K, WITH ABSENCE OR PRESENCE OF EFFUSION (GRADED 0-3)

Grade of Effusion .. ..	0	1	2	3
No. of Subjects .. ..	26	10	14	19
Range .. .. .	0.020-0.175	0.039-0.111	0.026-0.185	0.025-0.191
Mean .. .. .	0.059	0.069	0.087	0.071

activity grading. The only large effusions present were found in activity Groups 2 and 3. Fig. 3 correlates clearance value and effusion grading. When no effusion was present over 90 per cent. of the clearance constants fell within the normal range, and in Groups 1 and 3 approximately 20 to 25 per cent. of the clearance values were abnormally high. In Group 2 (moderate effusion), on the other hand, approximately 50 per cent. of the clearance constants were beyond the range of normal knees. It is therefore clear that the very large effusions are not associated with very high clearance values (Table II).

In considering the distribution of effusions in the disease activity groups, using the  $\chi^2$  formula, no significant correlation was found between the clearance constant and the grade of effusion except in disease activity Grade 2. In this group, of the eighteen subjects who had clearance constants

within the range of normal ( $<0.090$ ), ten had Grade 3 effusions, and four had Grade 2 effusions, whilst in the nine subjects with clearance values outside the range of normal, none had Grade 3 effusions and six had Grade 2 effusions. This difference is statistically significant ( $P>0.02$ ).

These findings indicate that the presence of a large effusion may modify the rate of sodium clearance from the joint, or that the circulation of active joints with large effusions is reduced by comparison with similar joints with smaller effusions. The presence of a large or chronic effusion may also affect synovial permeability. It is probable also that the size of the effusion unduly influenced our clinical grading of the knee, the tendency being to give them too high an activity grading. In retrospect we consider that our activity index would have been more reliable had "effusion" been omitted.

TABLE III  
CLEARANCE CONSTANT, K, OF FIVE PAIRS OF KNEES

Patient No.	Measurement No.	Right		Left	
		K	Grade of Disease	K	Grade of Disease
1	93	0.065	0	0.060	0
2	94	0.065	0	0.093	1
3	95	0.102	3	0.117	3
4	96	0.185	3	0.050	1
5	97	0.048	0	0.034	0

**Pairs of Knees.**—The clearance from pairs of knees was measured simultaneously in five subjects by a single counter technique. Table III shows a clear correlation between local disease activity and clearance rate in the pairs of knees; where both knees were at the same clinical stage, clearance values were fairly symmetrical and within the appropriate range for the stage of activity. In pairs where one knee was more actively involved, that knee had the higher clearance constant.

Fig. 4 shows the clearance curves simultaneously recorded from the two knees of a single subject, each knee being at a different stage of clinical activity. The clearance constants are markedly different, being much higher in the more severely involved knee.

**Repetition of Clearance Estimation.**—The clearance was measured at intervals varying from 1 to 12 weeks in nine subjects. Table IV shows that the clearance constant varied considerably in three subjects who showed no obvious changes in the grade of local disease activity. Both large increases and large decreases were found (e.g. 0.178-0.105, and 0.026-0.126). Two subjects showed no major changes.

In the five subjects in whom clinical improvement of the joint was observed, sharp decreases in clearance were found. One of these subjects was followed over a longer period and the clearance was measured again when the knee was deteriorating; on this occasion the clearance constant was found to be markedly increased (Patient 6 in Table IV). As might be expected over this period (1 to 12 weeks)

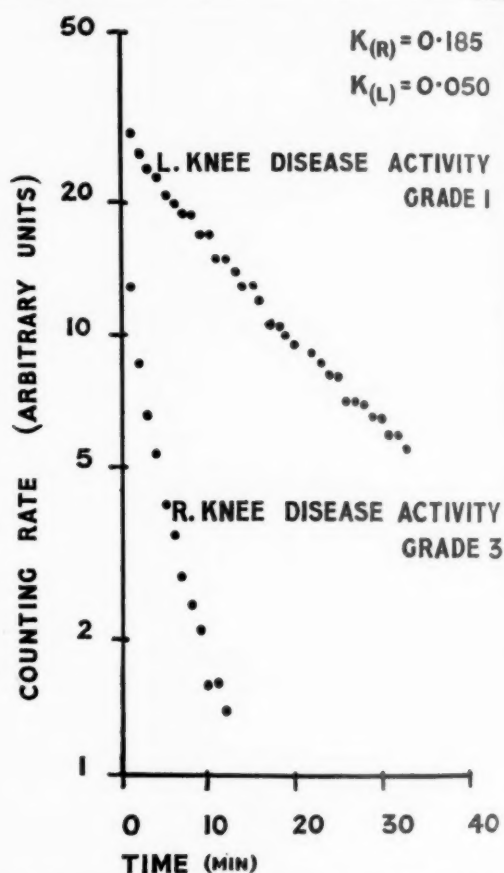


Fig. 4.—Clearance curves from both knee joints in a subject with rheumatoid arthritis, the knees being at different stages of disease activity.

TABLE IV  
INTERVAL CLEARANCE CONSTANT (K) OF KNEE JOINTS IN NINE PATIENTS

Patient No.	Measurement No.			Initial K		Interval (wks)	Second K		Interval (wks)	Third K	
	a	b	c	Grade	a		Grade	b		Grade	c
1	95	143		3	0.102	12	2	0.069			
2	103	140		2	0.101	10	1	0.056			
3	100	135		3	0.191	8	2	0.035			
4	101	148		3	0.104	12	3	0.111			
5	102	149		2	0.026	12	2	0.126			
6	115	131		2	0.175	4	1	0.043	8	2	0.131
7	99	151	160	0	0.041	12	0	0.067			
8	238	240		0	0.051	1	0	0.059			
9	220	221		2	0.178	1	2	0.105			
Mean	..	..	..	1.9	0.106	8	1.44	0.074	8	2	0.131

the patients improved, and this is shown by a fall in the mean local activity grading in Table IV, from 1.9 to 1.44. In the same period there was a comparable fall in the mean clearance constant, from 0.106 to 0.074.

**Intra-Articular Hydrocortisone.**—In thirteen subjects the effect of hydrocortisone injections into the joint was studied. The clearance from the knee joint was first measured (and these values included in the main series), and immediately afterwards 50 mg. hydrocortisone acetate acid free was injected into the joint without a local anaesthetic. In four subjects 1,000 units "hyalase" were given at the same time. The clearance was measured again in one week. In one subject the measurement was made after 24 hours, and in this case a major fall in clearance from 0.178 to 0.048 coincided with a good clinical response (Fig. 5).

On the whole the second clearance constant was decreased in comparison with the initial value, although one subject showed a rise of over 100 per cent. (0.050 to 0.119) with no evidence of clinical deterioration in the knee; in fact the joint was clinically improved. Eight subjects showed changes of less than  $\pm 20$  per cent., and the other four showed major decreases.

Table V shows, however, that in the three subjects who did not improve with the local hydrocortisone there were only small increases in the clearance constants. By contrast, the two subjects who were "much improved", both show major decreases in clearance.

**General Activity of the Disease.**—The erythrocyte sedimentation rate was recorded in all patients within one week of the sodium clearance measurement. This can be considered as a very approximate

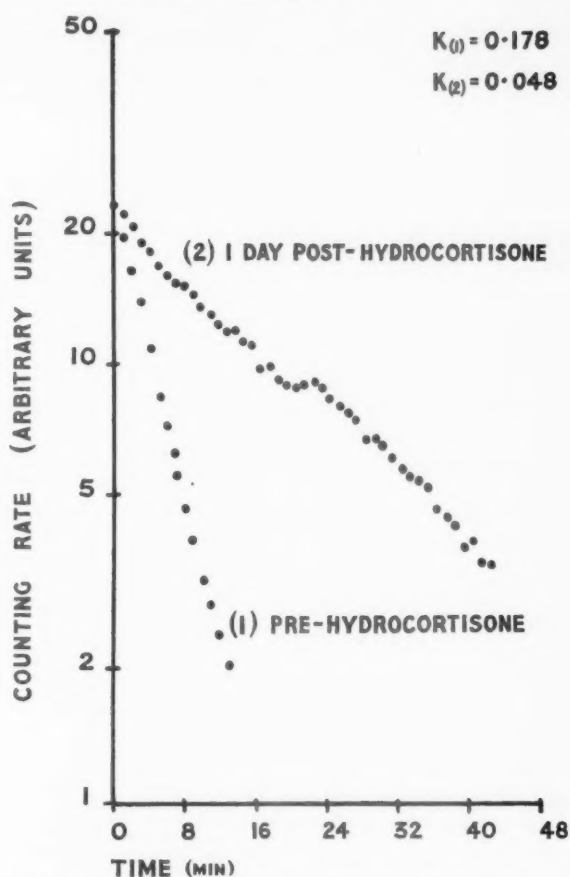


Fig. 5.—Clearance curves from the knee joint of a subject with rheumatoid arthritis before and 1 day after an intra-articular injection of 50 mg. hydrocortisone.

index of the general activity of the disease. Plotting erythrocyte sedimentation rate against the clearance constant gave a randomly scattered graph, with no

TABLE V  
EFFECT ON CLEARANCE FROM KNEE JOINT OF 50 mg. HYDROCORTISONE

Patient No.	Measurement No.		Initial K		Interval (wks)	Second K	Clinical Result
	a	b	Grade of Activity	a		b	
1	221	224	2	0.105	1	0.119	No change
2	225	226	2	0.178	1/7	0.048	Improved
3	228	231	3	0.076	1	0.068	Improved
4	229	230	3	0.050	1	0.119	Improved
5	232	234	2	0.119	1	0.036	Improved
6	227	233	2	0.045	2	0.039	Improved
7	236	241	3	0.090	1	0.047	Much improved
8	239	243	3	0.051	1	0.045	Improved
9	240	244	0	0.059	1	0.073	No change
10	245*	247	3	0.067	1	0.025	Much improved
11	246*	249	2	0.067	1	0.073	No change
12	256*	253	2	0.039	1	0.033	Improved
13	251*	252	2	0.042	1	0.044	Improved
Mean	..	..	..	0.076	..	0.058	..

\* 1,000 units "hyalase" given simultaneously with the hydrocortisone.



statistically significant correlation, which suggests that the clearance depends on local factors in the joint and not on the general disease activity.

### Discussion

The methods available for studying circulatory changes in joints are complicated and subject to criticism. The venous occlusion plethysmograph, with adrenaline iontophoresis to suppress skin circulation, is fairly satisfactory, but complicated in use (Bonney, Hughes, and Janus, 1952), and is difficult to use on painful joints. Extensive use has been made of intra-articular temperature measurements to study and compare changes in the knee joint in rheumatoid arthritis and osteo-arthritis (Hollander, Stoner, Brown, and De Moor, 1951; Hollander and Moore, 1956), and also to study the effect of intra-articular hydrocortisone in these conditions. The authors recognize the limitations of the method and the difficulty in interpreting results, and it has been shown by plethysmography (Bonney, Hughes, and Janus, 1952) that large alterations in blood flow can occur with only small changes in deep temperature, because of the stabilizing effect of the increased circulation at higher temperatures.

The radioactive sodium clearance technique is relatively convenient and simple, and we have shown in our earlier work (Harris and Millard, 1956) that the removal of sodium from the normal joint is influenced by factors which affect the blood supply of the joint. Ahlström, Gedda, and Hedberg (1956) have used the clearance of radioactive iodine-labelled serum albumin to study the difference between clinically normal and affected rheumatoid knee joints. Their results, using this large molecule, agree generally with ours, and, though the clearance values they found are much less than ours, the difference they found between active and inactive joints was similar to ours. They studied ten polyarthritics of varying degrees of activity, seven with and three without clinical changes in the knees. Between 2 and 22 mg. albumin, labelled with  $I^{131}$  and containing the equivalent of 15 to 20 microcuries, were injected intra-articularly and followed by a scintillation-counter and scaler. The clearance rate from the active knees was higher than that for normal knees. The highest clearance rate was found in a thickened knee without effusion in a subject with only a moderately raised erythrocyte sedimentation rate. They also studied the effects of intra-articular hydrocortisone in three subjects, and all showed a tendency to slow down towards normal values.

Our experiments clearly show that local factors in the joint itself, in contrast to the general state

of the disease, are the major influences on the sodium clearance.

In the pairs of knees studied simultaneously when the knees were at different stages of local activity, the more severely involved knees showed the greater clearance values. Intra-articular hydrocortisone, which produces only localized clinical effects, usually reduced the sodium clearance. However, we have shown that the local sodium clearance may vary after an interval without any obvious change in the joint, and there is also a wide variation in clearance from joints at the same stage of clinical activity. Also three subjects showed a complex curve for which we can offer no explanation. These are important factors limiting the value of the method.

The results in general were much as expected. It is well known that the active rheumatoid joint has a hyperaemic synovial membrane and that after the intra-articular injection of hydrocortisone both this and the intra-articular temperature return towards normal levels. These facts, with our observations of the local as opposed to the systemic factors involved, indicate that the sodium clearance technique is chiefly useful in measuring the total circulation and blood supply of the joint.

### Summary

(1) The rate of removal of radioactive sodium from the knee joint has been studied in 69 knees of patients with rheumatoid arthritis, defined as polyarthritis affecting three or more joints for at least 3 months without other discernible cause.

(2) The results show that, as in normal controls, the clearance from the joint is exponential; a single straight clearance line was obtained in 63 out of 69 experiments when the counting rate was plotted semi-logarithmically against time.

(3) The clearance rate was found to vary widely, the range in rheumatoid knees with little local disease activity or none being the same as in normal control knees.

Normal knees: Mean  $K=0.051$  (range 0.02 to 0.090).

Knees showing only minor disease activity: Mean  $K=0.057$  (range 0.032 to 0.090).

(4) The clearance rate for knees showing more severe local disease activity varied more widely and was generally higher.

Knees severely involved: Mean  $K=0.106$  (range 0.048 to 0.191).

(5) In subjects in whom the two knees were at different stages of disease activity, the sodium clearance was higher in the knee which was more severely involved.

(6) The effect of intra-articular hydrocortisone on sodium clearance was studied in thirteen knees at intervals of from 1 to 14 days; in general a reduction in the clearance rate towards normal values was found.

(7) The technique seems to be useful in studying circulatory changes in the knee joint, and could be used for screening potentially active drugs.

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## Elimination du radioiodium de l'articulation du genou dans l'arthrite rhumatoïdale

## RÉSUMÉ

(1) Le taux d'élimination du sodium radioactif de l'articulation du genou fut étudié dans 69 genoux des malades atteints d'arthrite rhumatoïdale, définie comme polyarthrite impliquant trois articulations ou plus, existant depuis au moins 3 mois et ne connaissant pas de cause apparente.

(2) Les résultats montrent que l'élimination articulaire suit une courbe exponentielle, comme chez des témoins normaux; une seule ligne droite d'élimination fut obtenue dans 63 sur 69 épreuves par un tracé semi-logarithmique de la fréquence numérique en fonction du temps.

(3) On a trouvé de grandes variations dans le taux d'élimination, les chiffres pour les genoux rhumatismaux manifestant peu ou pas d'activité morbide étant les mêmes que ceux pour les genoux normaux.

Genoux normaux: Moyenne  $K=0,051$  (étendue: 0,02-0,090). Genoux manifestant peu d'activité morbide: Moyenne  $K=0,057$  (étendue: 0,032-0,090).

(4) Le taux d'élimination pour les genoux manifestant

une activité morbide locale plus sévère était plus variable et généralement plus élevé.

Genoux severement impliqués: Moyenne  $K=0,106$ , (étendue: 0,048-0,191).

(5) Chez des sujets chez qui l'un des deux genoux était plus atteint que l'autre, l'élimination du sodium était plus intense dans l'articulation plus sévèrement impliquée.

(6) On a étudié l'effet d'hydrocortisone intra-articulaire sur l'élimination du sodium dans treize genoux par intervalles de un à 14 jours; on a trouvé qu'en général le taux d'élimination tendait à diminuer et à revenir à des chiffres normaux.

(7) Ce procédé paraît être utile dans l'étude des altérations de la circulation dans l'articulation du genou et pourrait être employé pour essayer des médicaments potentiellement actifs.

## Eliminación del sodio radioactivo de la articulación de la rodilla en la artritis reumatoide

## SUMARIO

(1) La tasa de eliminación del sodio radioactivo de la articulación de la rodilla fué estudiada en 69 rodillas de enfermos con artritis reumatoide, definida como poliartritis implicando tres articulaciones o más, en existencia desde 3 meses al menos y no manifestando causa aparente.

(2) Los resultados muestran que la eliminación articular sigue una curva exponencial, como en los testigos normales; se obtuvo una sola línea recta en 63 de los 69 experimentos por un trazado semi-logarítmico de la frecuencia numérica en función del tiempo.

(3) Se encontraron grandes variaciones en la tasa de eliminación; las cifras para rodillas reumáticas con poca o ninguna actividad mórbida fueron las mismas que para rodillas normales.

Rodillas normales: Media  $K=0,051$  (extensión: 0,02-0,090). Rodillas con poca actividad mórbida: Media  $K=0,057$  (extensión: 0,032-0,090).

(4) La tasa de eliminación para las rodillas manifestando una actividad mórbida local severa fué más variable y generalmente mayor.

Rodillas severamente implicadas: Media  $K=0,106$  (extensión: 0,048-0,191).

(5) En sujetos en que las rodillas se encontraban en etapas diferentes de actividad mórbida, la tasa de eliminación fué mayor en la rodilla más severamente implicada.

(6) Se estudió el efecto de hidrocortisona intra-articular sobre la eliminación del sodio en trece rodillas a intervalos de uno a 14 días; generalmente hubo reducción y retorno a lo normal de la tasa de eliminación.

(7) Este procedimiento parece útil en el estudio de las alteraciones circulatorias de la articulación de la rodilla y se puede emplear para ensayar medicamentos potencialmente activos.

## OBSERVATIONS ON THE SHRINK TEMPERATURE OF COLLAGEN AND ITS VARIATIONS WITH AGE AND DISEASE

BY

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The shrinkage temperature of collagen is related to its stability. When shrinkage takes place, it is thought that the hydrothermal agitation at this temperature is sufficient to overcome the forces, chiefly hydrogen bonds, which hold together the polypeptide chains. When stability is reduced by removal of hydrogen bonds with hydrogen bond breakers or by chemical damage, less energy is required to force the chains apart and so the shrink temperature is reduced. This is also paralleled by reduced resistance to the action of trypsin-like enzymes. Conversely, the introduction of new cross links into collagen, as in tanning, will increase enzyme resistance and the shrink temperature.

The different forms of collagen, soluble and insoluble, which occur together in native collagen, vary somewhat in their stability. Banga, Baló, and Szabó (1956) have suggested that the soluble has a stabilizing effect on the insoluble. In addition, polysaccharides and non-collagen proteins are concerned in the biogenesis of collagen fibres and their development into fully mature collagen (Bowes and Kenten, 1950; Partridge, 1948; Jackson, 1953). These constituents, always present in intimate association with native collagen, are probably important in determining the final stability and low turnover rate characteristic of fully mature collagen. It was therefore thought of interest to examine the shrink temperatures of human tissues of different ages to ascertain whether there were any age trends, and, if so, to correlate them with those changes in the various constituents which are known to take place with development and ageing. Further, since collagen in the uterus is rapidly deposited during pregnancy and rapidly absorbed after parturition (Harkness and Harkness, 1954), a feature which distinguishes this from collagen of other tissues and organs, the shrink temperature of uterine collagen from the uterus of various ages and in pregnancy was therefore of special interest.

In rheumatoid arthritis there is evidence, derived from electron microscopy, x-ray diffraction (Kellgren, Ball, Astbury, Reed, and Beighton, 1951; Kellgren, 1952), and histological studies (Glynn and Reading, 1956), that collagen fibres have suffered damage. We therefore thought it desirable to examine this and tissue from other "collagen disease" for any alteration in shrink temperature.

Much of the data on shrink temperature has been derived from species other than man. Further, many experiments have been carried out on such materials as hide powder which have probably become so altered as a result of preparation that the tissue finally examined could hardly be regarded as normal. Small but significant changes in shrink temperatures can occur after relatively mild treatments. Consequently, as far as untreated tissues were concerned, we considered it important to measure their shrink temperatures as soon as possible after collection, avoiding any pre-treatments such as washing, solvent extraction or prolonged storage. Also, since comparatively few observations have been made on human tissue, and since some of the data on non-human tissue are unreliable for reasons already mentioned and sometimes conflicting, a number of problems, such as the effect of hydrogen bond breakers were re-examined using fresh human tissue. For a few experiments, animal tissue was also used.

We have chosen normal saline in which to measure shrink temperatures since this appeared to be appropriate physiologically. It was found that the shrink temperature in saline was lower than that in water and was identical for different fibres in any given specimen. It was necessary to carry out shrink temperature measurements in a micro-apparatus when dealing with biopsied tissue available in only small amounts, and this method was used in most of the experiments described here.



## Methods

## (1) Shrink Temperature Measurement

(a) *Macro Method*.—This method was used only for a few measurements in the earlier part of this work. A strip of tissue 1-1.5 cm. was inserted into the lower end of a Westergren erythrocyte sedimentation rate tube. This was immersed in a beaker of water which was gradually heated. The temperatures at which the tissues started and finished shrinkage were recorded.

(b) *Micro Method*.—Small fibres teased out from the tissue immersed in physiological saline were allowed to rise up a capillary melting point tube, one end of which was then sealed. The tube and contents were placed in the micro-melting point apparatus (Gallenkamp) and the fibres observed under low magnification ( $\times 60$ ). By means of a rheostat in the circuit, the voltage applied across the heating element could be controlled up to a maximum of 6 volts. In this way, the heating was suitably controlled so that the rise of temperature was never greater than  $2^{\circ}\text{C}$ . per minute. Temperatures at which fibres started and finished shrinking were recorded. These are designated  $T_{s1}$  and  $T_{s2}$  respectively, and  $T_s$  refers to the complete range of shrinkage ( $T_{s1}$  to  $T_{s2}$ ). All temperatures are expressed in  $^{\circ}\text{C}$ .

## (2) Analyses

(a) *Nitrogen* was estimated by the permanganate modification of the micro Kjeldahl method (Beet, 1955).

(b) *Hydroxyproline* was estimated in hydrolysates according to the method of Neuman and Logan (1950).

(c) *Salicylate* in extracts was determined by the method of Trinder (1954).

(d) *Fluorescence in Ultra-Violet Light* was observed macroscopically under the high-pressure

mercury lamp (Hanovia Model XI) with Woods glass filter.

## (3) Materials

(a) *Tissues*.—Human tissue obtained at autopsy or at operation was examined in most cases immediately after collection, and, occasionally after being kept overnight at  $0-4^{\circ}\text{C}$ . Overnight storage at this temperature had no effect on the shrink temperature, whereas storage at  $-20^{\circ}\text{C}$ . caused a lowering of as much as  $4^{\circ}\text{C}$ . in the  $T_{s1}$  of many of the specimens. Apart from uteri, dura mater or fascia lata were used in all comparative work, as in any one individual these had a similar shrink temperature, and, except where indicated, all tissues were from patients not suffering from any "collagen disease".

(b) *Acid Soluble Collagen* was prepared by salt precipitation of citrate extracts of rabbit skins, based on the method described by Bowes, Elliott, and Moss (1955).

## Results

## I. Various Extraction Procedures

(a) *Effect of Hyaluronidase and Periodate on  $T_s$* .—Rabbit fascia and tendon and rat fascia and tail tendon (kept overnight at  $-20^{\circ}\text{C}$ .) were treated with hyaluronidase or periodate. For the former treatment the tissue was incubated at  $37^{\circ}\text{C}$ . overnight in acetate buffer, 0.1 M, pH 5.2, containing 1 mg./ml. "Hyalase" (Benger). Controls consisted of tissue incubated in acetate buffer without hyalase. The tissue residues were washed three times with normal saline and then three times with water. For the periodate treatment the tissue was allowed to stand at room temperature for 17 hours in a solution of sodium periodate (0.5 per cent.) in acetate buffer (0.1 M, pH 4.0). Controls were similarly treated in the acetate buffer without periodate. The  $T_s$  by the macro method, in water, is recorded in Table I, which demonstrates that those of the treated and control tissues were equally lowered by both treatments.

TABLE I

EFFECT OF HYALURONIDASE AND PERIODATE ON  $T_s$ 

Tissue	Before Treatment	Hyaluronidase		Periodate	
		Treated	Control (Buffer only)	Treated	Control (Buffer only)
Rabbit Fascia .. .. .	67-70	58-64	54-58	52-58	52-60
Rabbit Tendon .. .. .	62-66	56-60	56-60	49-50	47-50
Rat Fascia .. .. .	62-65	54-57	52-57	52-54	48-53
Rat Tail Tendon .. .. .	63-66	51-54	47-52	42-45	40-44



(b) *Effect of Buffers and Strong Alkali on Ts.*—Pieces of fascia from a stillborn child and from a 63-year-old man, which had been stored for some weeks in a frozen state, were immersed for 3 days at room temperature in water, M/15 phosphate of pH 7, M/5 citrate of pH 4, and M/5 KOH. It was noted that the KOH-treated tissue was greatly swollen. The tissues were then washed three times with water and then three times with saline and the Ts was determined (Table II). The Ts figures of the water control in the adult specimen were slightly low because the tissue had been frozen. Only KOH treatment lowered the Ts, the effect on the young tissue being greater.

TABLE II  
Ts AFTER EXTRACTION WITH BUFFERS OR STRONG ALKALI

Treatment of Tissue	Source of Tissue	
	Full-Term Foetus	Man Aged 63 years
H <sub>2</sub> O Control .. .. .	55-61	58-65
Phosphate pH 7.M/15 .. ..	54-61	58-65
Citrate pH 4.M/5 .. .. .	54-61	57-65
KOH M/5 .. .. .	41-52	52-61

II. Effect of Hydrogen Bond Breakers

(a) *Fascia Lata from One Individual.*—The tissue was obtained at autopsy from a woman aged 25 (dying from cerebral haemorrhage due to malignant hypertension). Small pieces were immersed for 4 days at room temperature in solutions of various reagents of 2 M strength except potassium phenol sulphonate which could not be made stronger than 1 M, water-saturated phenol, and phenol-saturated water. The solutions were about pH 7.0 to brom-thymol blue indicator. The tissues were washed three times with water and then three times with saline. The resulting shrink temperatures in

saline by the micro method are recorded in Table III.

TABLE III  
Ts OF FASCIA LATA AFTER TREATMENT WITH VARIOUS REAGENTS

Treatment of Tissue	Ts (° C.)
H <sub>2</sub> O control .. .. .	61-66
KCNS 2M .. .. .	57-64
Urea 2M .. .. .	52-66
Phenol in H <sub>2</sub> O .. .. .	62-66
H <sub>2</sub> O in phenol .. .. .	35-63
Catechol 2M .. .. .	62-71
Na Anthranilate 2M .. .. .	59-66
K phenol sulphonate 1M .. .. .	62-66
Na Gentisate 2M .. .. .	37-63
NH <sub>4</sub> E.D.T.A. * 2M .. .. .	60-65
Butazolidine 2M .. .. .	56-66
Na Salicylate 2M .. .. .	32-62

\* Ethylene diamine tetra acetate.

After salicylate, the tissue appeared somewhat swollen in contrast to the other tissues. The greatest fall in Ts was obtained with salicylate, gentisate, and water-saturated phenol (*p*-amino salicylate was equally effective, see below).

(b) *Fascia Lata of Individuals of Different Ages.*—Tissues were all obtained at autopsy from patients who had not suffered from any connective tissue disease. Treatment in various reagents was carried out as described above and the results are shown in Table IV. From these results we draw the following conclusions:

- (i) The older the tissue the higher the Ts appears to be.
- (ii) The Ts of the younger tissue is lowered to a greater extent by all the hydrogen bond breakers, and, even those reagents without effect on the older specimens still had a distinct effect on the younger tissues.
- (iii) Salicylate and *p*-amino-salicylate lowered the Ts most.

III. Salicylate Experiments

(a) *Variation of Ts with Salicylate Concentration.*—Fascia lata from a 15-year-old girl who had died

TABLE IV  
Ts AFTER TREATMENT WITH HYDROGEN BOND BREAKERS OF FASCIA LATA FROM INDIVIDUALS OF VARIOUS AGES

Age	Before Treatment	H <sub>2</sub> O	Na <i>p</i> -amino Salicylate	Na Salicylate	Na Benzoate	Na <i>p</i> -amino Benzoate	NH <sub>4</sub> Sulphanilate
61 yrs .. .. .	63-67	63-68	54-68	48-62	63-67	63-67	62-67
15 yrs .. .. .	58-64	57-62	37-62	37-60	48-62	48-60	49-59
18 days .. .. .	55-61	56-62	28-49	28-43	37-59	39-57	40-61
Stillborn (full-term) ..	54-62	54-61	31-62	28-61	36-62	41-60	47-60
34-wk Foetus .. .. .	55-61	55-62	29-57	34-58	38-52	37-58	40-60

from Schönlein-Henoch purpura and glomerulonephritis was treated in doubling dilutions of sodium salicylate starting with 2 M for 4 days at room temperature. Shrink temperatures were determined after washing (as described above); the results are recorded in Fig. 1. Up to a concentration of 0.5 M there was no lowering of  $T_s$ . At higher concentrations there was a rapid fall of  $T_{s1}$ .

(b) *Variation of  $T_s$  with Incubation Temperature.*—The tissue was the same as that described in II(a). Samples were kept in 2 M salicylate for 4 days at 4°, 18°, 37°, and 56° C. The results are shown in Table V. The lowering was less at 4° than at 18° C. and those tissues treated at higher temperatures began shrinking at temperatures above those of the treatment.

(c) *Effect of Acid Treatment of Salicylate-Treated Tissue.*—The  $T_s$  of rabbit acid soluble collagen

was observed to be 41–45° C. Since 2 M salicylate lowered the  $T_s$  to this or lower figures, the following experiment was carried out to determine whether salicylate-treated tissue was similar in any other way to acid soluble collagen.

Fascia from an 18-day-old infant (initial  $T_s$  55–61° C.) which after treatment with 2 M salicylate for 4 days had  $T_s$  28–41° C., was then shaken with M/5 citrate buffer pH 4. After extraction, the  $T_s$  was raised to 34–48° C. The citrate supernatant was made alkaline with KOH, but there was no precipitate.

Acid soluble rabbit collagen ( $T_s$  41–45° C.) dissolved readily and completely in 2 M salicylate at room temperature. The solution was left at this temperature for 4 days, dialysed against distilled water, and made alkaline with KOH. No precipitation occurred. When another sample of acid soluble collagen was dissolved in citrate buffer, dialysed and made alkaline, it was re-precipitated.

(d) *To Test whether the Salicylate Effect on  $T_s$  was due to Swelling*

(i) *Effect of High Concentrations of Neutral Salts on the  $T_s$  of Salicylate-Treated Tissue.*—In one experiment, tissue which had been treated with 2M salicylate was washed with water. One portion was then treated with 2M  $\text{CaCl}_2$  solution for 4 days at room temperature, and another with saturated NaCl. Controls were tissues which were given the calcium chloride and sodium

TABLE V  
VARIATION OF  $T_s$  WITH TEMPERATURE OF  
SALICYLATE TREATMENT (2M)

Temperature of Treatment	$T_s$ after 2M Salicylate	$T_s$ of $\text{H}_2\text{O}$ Control
4° C.	52–62	61–66
18° C.	33–62	61–66
37° C.	38–56	62–66
56° C.	56–61	62–66

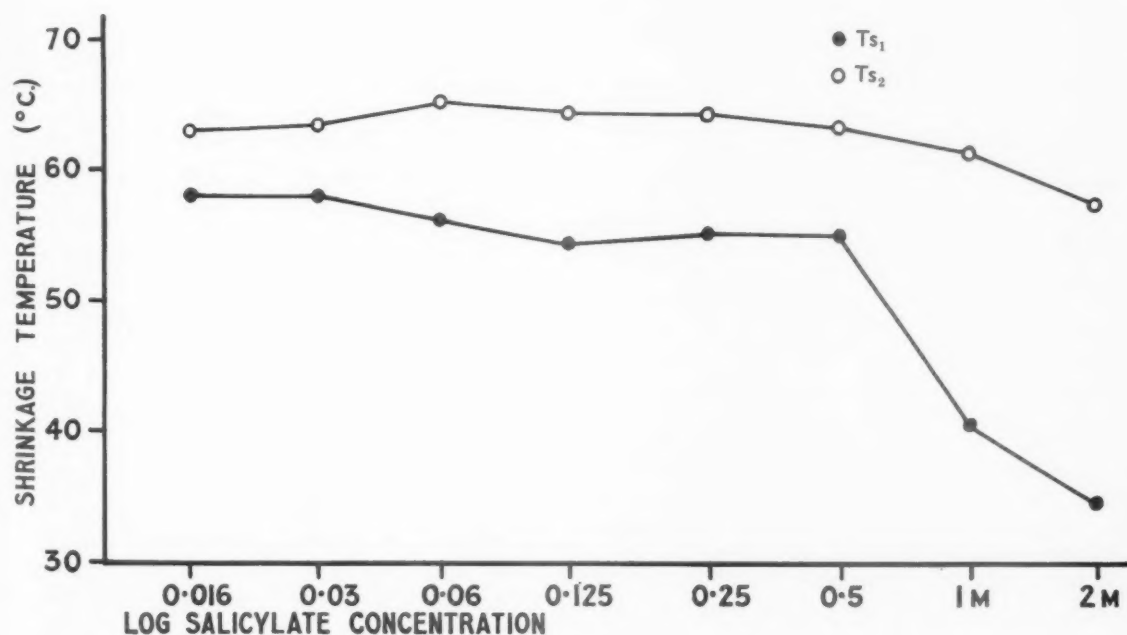


Fig. 1.—Variation of  $T_s$  with concentration of salicylate used in pre-treatment.

chloride treatments only. Shrinkage temperatures were measured after washing (Table VI).

TABLE VI  
EFFECT OF NEUTRAL SALTS ON  $T_s$  OF SALICYLATE  
TREATED AND CONTROL TISSUES

Salt Solution	Tissue Treated with Salicylate ( $T_s$ 33-62)	Tissue not Treated with Salicylate ( $T_s$ 54-64)
Saturated NaCl	29-63	55-62
CaCl <sub>2</sub> 2M	27-64	54-60

Tissue ( $T_s$  51-60° C.) was treated with 2M salicylate alone and 2M salicylate containing 10 per cent. NaCl for 4 days. There was little difference in the appearance of both specimens. The  $T_s$  after each treatment was identical (27-53° C.).

These experiments indicate that the presence of strong solutions of electrolytes, which prevent the uptake of water molecules, have little effect on the lowering of  $T_s$  by salicylate, and that treatment with strong salt solutions does not lower the  $T_s$  of fresh tissue.

(ii) *Water Content of Tissue before and after Salicylate Treatment.*—Three samples of tissues were treated in distilled water 1M and 2M salicylate respectively. After treatment the tissues were washed with water, lightly blotted with filter paper, and weighed. They were then reweighed after drying *in vacuo* over MgClO<sub>4</sub>. The amount of water in the salicylate-treated tissue was calculated from the increase in weight less the absorbed salicylate.\* The results are recorded in Table VII. The amount of water present in salicylate-treated tissue is similar to that present in untreated tissue.

TABLE VII  
WATER CONTENT OF SALICYLATE TREATED TISSUE  
COMPARED WITH UNTREATED TISSUE

Concentration of Salicylate	Loss of Weight on Drying (per cent.)	Estimated Salicylate Present (per cent.)	Water expressed as Percentage of Salicylate-free Wet Tissue
0	79	0	79
1M	76	13	79
2M	73	40	81

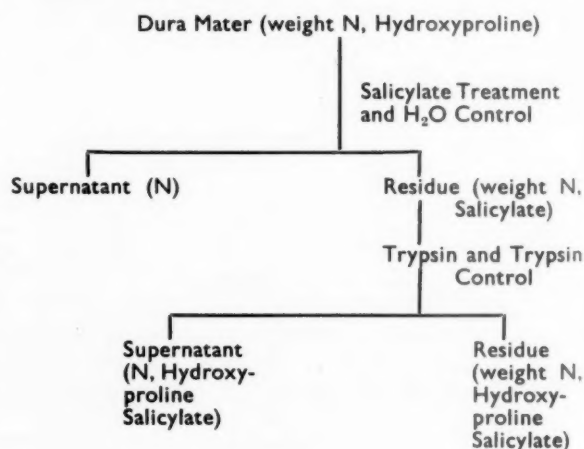
(e) *Measurement of  $T_s$  in Solutions of Various Concentrations of Salicylate and Potassium Thiocyanate.*—In these experiments, fibres from fresh tissue ( $T_s$  61-67° C.) were immersed and shrunk immediately in these solutions. Doubling dilutions of salicylate and thiocyanate from 2 M to 0.0078 M were used. The latter reagent was chosen because,

\* The latter figure was obtained on the same tissue in a later experiment (Table VIII).

by comparison with salicylate under the standard conditions already described (IIa), it had much less effect on  $T_s$ . In addition the tissues were left in the salicylate solutions for 5 days at room temperature before measuring  $T_s$  in these solutions. The results are shown in Fig. 2 (opposite) from which the following observations can be made:

- Under these conditions salicylate lowers the  $T_s$  much more than thiocyanate.
- When treated with 2M salicylate for 5 days, the  $T_{s1}$  determined in saline dropped from 61° to 38° C., whilst  $T_{s2}$  remained at 67° C.; under the present conditions the same effect on  $T_{s1}$  was produced by 0.5M salicylate, and  $T_{s2}$  began falling in 0.125M and continued to fall in increasing concentrations of salicylate.
- In the 5-day salicylate-treated tissue,  $T_{s1}$  was further decreased considerably but  $T_{s2}$  was not further affected.

(f) *Action of Trypsin on Salicylate-Treated Tissue.*—Two samples of dura mater from a male aged 63 were dried *in vacuo* over magnesium perchlorate and treated with 2 M and 1 M salicylate respectively for 4 days at room temperature. A third sample was similarly treated with distilled water. The tissues were then removed and washed with water, and the washings were added to their respective supernatants and made up to a suitable volume for analysis. The tissues were then dried, and weighed amounts were incubated with trypsin (Armour 2,820 units/mg.) 1 mg./ml. in 0.9 per cent. sodium bicarbonate or with bicarbonate alone at 37° C. for 17 hours. After washing as above, supernatants and washings were combined and made to volume. Residues were dried *in vacuo*. Analyses (N, hydroxyproline, salicylate) were carried out according to the scheme set out below (all weighings were dry weights):



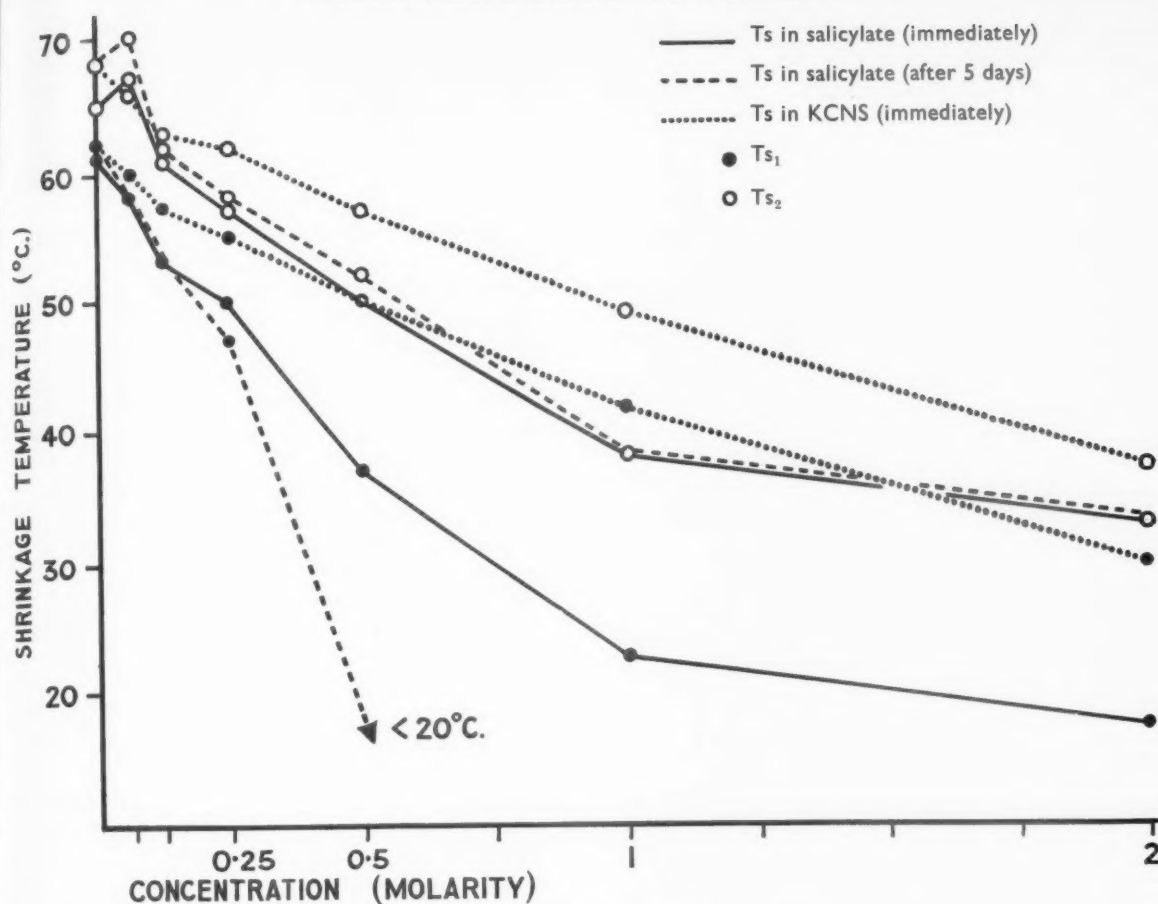


Fig. 2.—Ts in solutions of various concentrations of salicylate and thiocyanate.

The results are given in Table VIII. The salicylate recovered was calculated from the increase of dry weight of tissue after treatment, allowing for the protein extracted. The latter figure was computed

from the nitrogen in the salicylate extract, using the conversion factor of 6.25. The nitrogen figures were probably somewhat low because of the presence of large amounts of salicylate which required pro-

TABLE VIII  
ACTION OF TRYPSIN ON SALICYLATE-TREATED TISSUE

Salicylate Treatment				Trypsin Treatment of Salicylate-Treated Tissue							Control (Buffer Alone)				
Concentration	Ts	Per cent. Weight Change	Per cent. N Loss	Ts	Per cent. Weight Loss	Per cent. N Loss	Hydroxyproline			Per cent. Salicylate† Extracted	Per cent. Weight Loss	Per cent. N Loss	Hydroxyproline		Per cent. Salicylate† Extracted
							Per cent. Loss	N as per cent. total N in					Per cent. Loss	N as per cent. Total N in Supernatant	
								Residue	Supernatant*						
0	60-66	-15	5.9	60-66	14	10.6	<0.01	7.9	<0.01	—	10	2.3	<0.01	<0.01	—
1M	52-66	+ 9.5	1.7	56-64	27	21.0	0.78	8.3	0.28	72	16	2.4	<0.01	<0.01	96
2M	40-66	+39	0.9	43-64	71	56.5	47	7.0	4.34	82	28	4.4	0.74	0.84	69

\* For the untreated tissue the value was 6.6.

† Expressed as per cent. of that calculated to be present in the tissue after salicylate treatment (see Table VII).



longed digestion and relatively large amounts of permanganate for clearing in the Kjeldahl procedure. The figures for salicylate are therefore considered to be approximate.

The following conclusions can be drawn from the data in Tables VII and VIII:

- (i) Considerable amounts of salicylate remained on the tissue despite repeated washings, but most was extracted under the weak alkaline conditions of incubation. (It was found subsequently that substantially all salicylate could be extracted by prolonged (10 days) treatment with 0.9 per cent. bicarbonate at 37° C.) Salicylate therefore comprised most of the material extracted by the solutions in the trypsin control experiments and formed about one-third of that dissolved out by trypsin.
- (ii) Salicylate alone extracted small amounts of nitrogen, but progressively less with increasing concentration of salicylate.
- (iii) The untreated tissue contained about 80 per cent. collagen as calculated from hydroxyproline content, assuming 8.2 hydroxyproline N as percentage of total nitrogen for collagen. Therefore, about 20 per cent. of the tissue was non-collagen protein, and this, after 1M salicylate, was completely removed by trypsin as compared with only half removed by trypsin acting on the tissue which had had no salicylate. The hydroxyproline data indicate that the 20 per cent. protein extracted from the 1M salicylate-treated tissue by the trypsin contained very little collagen. Trypsin following 2M salicylate extracts much more nitrogen than after 1M pre-treatment and this further nitrogen appeared to be derived from the collagen itself.
- (iv) In bicarbonate alone, twice as much nitrogen was extracted from tissue treated with 2M salicylate than from untreated tissue or from that treated with 1M salicylate (4 per cent. compared with 2 per cent.). Also 10 per cent. of the bicarbonate extract after 2M salicylate was collagen and this represented 0.7 per cent. of the original collagen in the tissue.

- (v) Digestibility was not due to the shrinking of the collagen during the course of incubation. It does not appear likely that prolonged incubation caused shrinkage to occur at a lower temperature and therefore digestion to take place, since the residue after trypsin still had a similar low  $T_{s1}$ .

#### IV. Tissues of Different Ages

(a) *Variation of  $T_s$  with Age and the Effect of Salicylate.*—Shrink temperatures in saline were determined by the micro method. The samples were then treated with 2 M salicylate as already described, and the  $T_s$  of the washed tissue was again determined in saline. These results are recorded in Table IX. ( $T_{s2}$  after salicylate treatment is not recorded, since it was unaltered in about half the cases and in the remainder, with the exception of an 18-day-old infant, the fall was around 4° C.) By statistical analysis of some of the data for  $T_{s1}$  of the untreated tissues, the variance ratio,  $F$ , between the groups = 35.3; standard error for  $T_{s1}$  (single determination) = 1.33; the least significant difference of the means between groups = 1.43 ( $p=0.05$ ) for means of seven determinations in each group and is correspondingly less where the number in a group is greater than seven. For the  $T_{s1}$  of the salicylate-treated tissues,  $F$  between groups = 12.0; standard error (single determination) = 4.17; least significant difference of the means between groups of seven = 4.49, between groups of seven and eight = 4.36, and between groups of eight and eighteen = 3.57. From these results the following conclusions may be drawn:

- (i) Except between the age groups 15-25 and 26-44 years, the difference of means between groups is greater than 1.43, and it may be concluded therefore that in any two age groups, with the exception of those mentioned above, the  $T_{s1}$  is significantly higher in the older group. The  $T_{s2}$  figures clearly follow the same pattern and the same conclusions would apply.
- (ii) The statistical analysis of the  $T_{s1}$  salicylate

TABLE IX

VARIATION OF  $T_s$  WITH AGE AND EFFECT OF SALICYLATE

Age Group	$T_{s1}$		$T_{s2}$		$T_{s1}$ after Salicylate		No. of Cases
	Mean	Range	Mean	Range	Mean	Range	
Foeti 12-40 wks ..	54.4	53-55	60	59-62	28.7	24-34	7
0-14 yrs .. ..	57.7	55-59	63.9	61-67	29.8	28-33	12
15-25 yrs .. ..	59.8	57-62	65.7	64-68	31.1	27-37	7
26-44 yrs .. ..	59.1	57-61	66.2	65-67	35.3	32-47	8
45-88 yrs .. ..	61.2	59-63	67	66-68	38.5	30-48	18

figures show that, although the increase from one age group to the next was not large enough to reach the 5 per cent. significance level, there was a steady increase with age, and this overall increase is highly significant ( $F=12.0$ ).

(b) *Examination of Uteri.*—The  $T_s$  of uterine collagen was examined before and after 2 M salicylate treatment as in the previous section (Table X). The fibres examined were teased out from the myometrium of the body of the uterus. Of the age group below 45 years, one was aged 4 months and the remainder from 25-45 years, four of which were pregnant. Statistical analysis of the  $T_{s1}$  of untreated tissue gave the variance ratio  $F=14.41$ , standard error of  $T_{s1}=1.74$ , and the least significant difference  $=1.37$  for  $p=0.05$ . The standard error of the  $T_{s1}$  salicylate figures for a single determination was 2.46.

The following conclusions were drawn:

- (i) In the untreated tissue there appeared to be little variation of  $T_{s1}$  within each group but statistical analysis showed that the  $T_{s1}$  means differed in a highly significant way between the two groups.  $T_{s2}$  did not vary significantly between the groups.
  - (ii) By comparison with the data in Table IX, collagen from the uterus up to about the age of the menopause is seen to be closely similar, as regards hydrothermal stability, to foetal collagen. Uterine collagen of the older group, on the other hand, resembled the 0 to 14-year-old collagen.
  - (iii) After salicylate treatment the means between the two age groups of the  $T_{s1}$  were not significantly different.
- (c) *Fluorescence and Age.*—All tissues examined in the previous two sections were examined in ultraviolet light for fluorescence. No fluorescence was observed in any of the tissue from foeti or stillbirths. The only two samples obtained within the first year of life (4 and 11 months) fluoresced a weak purple. All the other tissues (4-year-old and over) fluoresced a brilliant white blue. This early manifestation of fluorescence in dura and fascia lata is not a feature of uterine collagen. Of the twelve

uterine specimens under 45 years of age, eight between the ages of 25-45, of whom four were pregnant, did not fluoresce, two (aged 4 months and 41 years) fluoresced a weak purple, and two (aged 44 and 45 years) a brilliant white-blue. All sixteen specimens of over 45 years of age also fluoresced brilliantly. The failure to fluoresce by the younger uteri was not due to quenching by other protein, since digestion with trypsin left a residue which was still non-fluorescent and which showed no alteration of  $T_s$ . Trypsin digestion of a fluorescent tissue did not affect its fluorescence or  $T_s$ .

## V. Pathological Tissue

(a) *Rheumatoid Nodules.*—Three specimens which were histologically typical rheumatoid nodules were obtained at biopsy. They consisted of a capsular area surrounding a tough white fibrous region in which were yellow necrotic foci. Fibres from these three areas were individually examined for  $T_s$ ,  $T_s$  after salicylate, and fluorescence (Table XI, overleaf). Different fibres from each area gave consistently repeatable readings.

From these results the following conclusions may be drawn:

- (i) In general, fibres from any one area of one nodule behaved similarly to fibres from the same area of the other nodules, but there were significant differences between each of the three areas.
- (ii) In the capsular area, the  $T_s$  of two were similar to the normal values of that age group (Table IX); the third was somewhat low. Salicylate produced a greater fall in  $T_{s1}$  as compared with normal and, in contrast with normal tissue,  $T_{s2}$  was also lowered.
- (iii) The greatest changes occurred in the tough fibrous area; the  $T_{s1}$  was lower even than that of the foetal group (Table IX), and the  $T_{s2}$  was lower than that of the capsular area. After salicylate, two had very low  $T_{s1}$  and that of the third was raised, and in view of the very small amount of shrinkage, the significance of these results is not clear.

TABLE X  
 $T_s$  OF HUMAN UTERI BEFORE AND AFTER 2M SALICYLATE

Age (yrs)	$T_{s1}$		$T_{s2}$		$T_{s1}$ after Salicylate		No. of Cases
	Mean	Range	Mean	Range	Mean	Range	
Under 45* .. ..	55.2	53-57	63.4	61-67	32.1	28-35	12
Over 45 .. ..	57.8	55-61	63.1	61-67	32.5	28-36	16

\* Full term of pregnancy in four cases.

TABLE XI

TS OF RHEUMATOID NODULES BEFORE AND AFTER 2M SALICYLATE AND PRESENCE OF FLUORESCENCE

Nodule	Capsular			Tough Fibrous			Yellow Necrotic		
	Fluorescence	Ts	Ts after Salicylate	Fluorescence	Ts	Ts after Salicylate	Fluorescence	Ts	Ts after Salicylate
I (age 46)	Brilliant white-blue	58-64	34-58	Weak purple	51-61	57-61*	Very weak purple	54-64	43-61*
II (age 49)	Brilliant white-blue	60-66	30-60	Weak purple	52-64	31-59*	Weak white-blue	55-60	36-60*
III (age 55)	Brilliant white-blue	60-67	28-63	Very weak purple	53-61	28-55*	Very weak purple	55-65	55-65*

\* Very little shrinkage.

(iv) The fibres from the yellow necrotic area had a Ts similar to that of foetal tissue and appeared to be intermediate in this respect between the capsular and tough fibrous areas. After salicylate the results again, as with the tough fibrous area, were difficult to assess.

(v) Whereas the capsular area fluoresced brilliantly like normal non-foetal fascia, all fibres from the other two areas fluoresced only very weakly.

(b) *Fascia from Rheumatoid and Other "Collagen" Diseases.*—Samples of fascia were obtained at operation or at autopsy from twelve cases of rheumatoid arthritis, two cases of rheumatic fever, one case of dermatomyositis, and one case of periarteritis nodosa. Shrinkage temperature before and after salicylate are recorded in Table XII. All these specimens showed the normal brilliant white-blue fluorescence.

Because of the small number of samples, no statistical analysis has been attempted. In general, all the tissues appeared to be similar to the normal tissues (Table IX). However, in two cases, one of rheumatoid arthritis and one of rheumatic fever, the Ts<sub>2</sub>, 71° and 72° C. respectively, was much higher than that of any other tissues examined. Both tissues were obtained at biopsy; the former patient

was receiving penicillin 300,000 units twice a day and the latter was receiving salicylates.

### Discussion

#### Shrink Temperature and Stabilizing Cross Linkage.

—Several types of cross-link are theoretically available to account for the thermal stability of collagen, but it is doubtful whether the majority of these contribute to any great extent. Gustavson (1956a) divides these linkages into directed and non-directed, and of the directed linkages the most important are salt links and hydrogen bonds. Disruption of the salt links by  $\beta$ -naphthol sulphonic acid reduces the Ts by only 14-16° C. (Gustavson, 1956b), whereas powerful hydrogen bond breakers, such as salicylate, reduce it by as much as 30° C. From this simple computation, it would appear that hydrogen bonds are of much greater importance than salt linkages. The virtual absence of thio-amino acids from collagen excludes the possibility of sulphur bridges playing any significant role. The presence of ester and other linkages has been suggested, but here again, on purely numerical grounds, these are unlikely to make more than a small contribution to the stability of the molecule. The presence of

TABLE XII

TS OF FASCIA FROM RHEUMATOID AND OTHER "COLLAGEN" DISEASES BEFORE AND AFTER 2M SALICYLATE

Disease	Age Group (yrs)	No. of Cases	Ts <sub>1</sub>		Ts <sub>2</sub>		Ts <sub>1</sub> after Salicylate	
			Mean	Range	Mean	Range	Mean	Range
Rheumatoid Arthritis	0-14	4	58	57-59	66	62-71	29	28-30
	26-44	2	58.5	58-59	66	65-67	30	27-33
	45 and Over	6	59	57-62	67	66-68	31.5	28-34
Rheumatic Fever	13	1	58	—	62	—	33	—
	23	1	56	—	72	—	37	—
Dermatomyositis	4	1	58	—	67	—	33	—
Periarteritis nodosa	63	1	60	—	67	—	39	—



an irreducible minimum of 0.5 per cent. polysaccharide in even the purest preparation of collagen suggests an important role for these substances as cementing or stabilizing agents. Jackson (1953), in particular, has emphasized the importance of such substances (*e.g.* chondroitin sulphate). The marked reduction in  $T_s$  of rat tail tendon (Jackson, 1954) following treatment with hyaluronidase or following oxidation with periodate which he observed strongly supports this hypothesis. We, however, have completely failed to confirm these results in similar experiments. The reduction of  $T_s$  of 12° C. following treatment with hyaluronidase was less than that observed when similar material was treated in the buffer alone (pH 5.2). Similarly, the marked reduction observed in  $T_s$  after periodate treatment was no greater than that of the control material in the buffer alone at pH 4.0. In view of the recent report of Meyer, Davidson, Linker, and Hoffman (1956) that the chondroitin sulphate present in tendon is predominantly Type B, *i.e.* the variety which contains iduronic acid and is insensitive to testicular hyaluronidase, it is not surprising that the effect of this enzyme is no greater than the buffer alone. The role of the mucopolysaccharides has also been questioned by Courts (personal communication). In his study of the collagen-gelatin transformation, he has shown that, during the liming process, considerable quantities of polysaccharides are removed, but, in the alternative process of acid pretreatment, which also facilitates the transformation to about the same degree, the whole of the mucopolysaccharide remains behind. This, as Courts points out, does not necessarily exclude the polysaccharide from playing a stabilizing role, since it is conceivable that the acid pretreatment might only disrupt one end of the hypothetical polysaccharide bridge.

Comparison of Tables I and II shows an apparent difference in response between human and other mammalian collagen to acid buffers at pH 4. This however, is probably not due to the difference in species but to the different nature of the buffers used. Acetate is known to possess a considerable lyotropic effect, presumably by virtue of its power to rupture hydrogen bonds (Gustavson, 1943).

With few exceptions, the effect of hydrogen bond breakers on  $T_s$  is confined to its influence on the temperature at which shrinkage begins, but has little effect upon the upper limit of  $T_s$ . This suggests either that the bonds responsible for stability at the higher temperatures are not hydrogen bonds, or that they are more concentrated in these more resistant regions. They are, nevertheless, moderately thermolabile, since they are apparently disrupted at between

60° and 70° C. Failure of extraction with phosphate buffer at pH 7, or citrate buffer at pH 4, to reduce the  $T_s$  (Table II) excludes both the alkali soluble and acid soluble forms of collagen from the group of important stabilizing agents. Extractions with strong alkali reduced not only the  $T_{s1}$  but also the  $T_{s2}$ , indicating that the bonds responsible for the upper limit of  $T_s$  are here also affected in addition to the rupture of hydrogen bonds. It is especially interesting in this regard to note that such treatment extracts a significant proportion of the mucopolysaccharides (Consden and Bird, 1954; Bird and Consden, 1955; Bowes, Elliott, and Moss, 1956) initially present, though it must be admitted that rupture of peptide bonds and loss of amide nitrogen also result from this treatment. The swelling which the tissue undergoes as a result of such strong alkaline treatment far exceeds that which occurs even with the most powerful hydrogen bond breakers, which may be regarded as further evidence for the disruption of other restricting bonds (Bowes and Kenten, 1950).

**Effect on Shrink Temperature of Pretreatment with Salicylate.**—The potent effect of salicylates on  $T_s$  has already been described by Lennox (1949) on sheep skin. He carried out his  $T_s$  estimations in solutions of salicylate so that his results are not comparable to ours in which the tissue was thoroughly washed after salicylate treatment and the  $T_s$  determined in saline. In the single experiment in which we determined the  $T_s$  in solutions of salicylates, our results were similar to his. The bulk of previous work on the influence of lyotropic agents on collagen has been carried out using hide powder. It is now appreciated that results with hide powder cannot necessarily be extrapolated to native collagen, since considerable denaturation occurs in the process of producing the powder. The different hydrogen bond breakers vary enormously in their ability to reduce the  $T_s$  in equi-molar solutions. In general, those which disrupt the hydrogen bonds by offering a competing hydrogen atom are more potent than those which are hydrogen acceptors.

The swelling of collagen after treatment with 2 M salicylate is not comparable to that which occurs in strong alkali. The latter is almost entirely due to the uptake of water, but the swelling in salicylate is entirely due to the uptake of salicylate itself as is shown in Table VII, where the water content, expressed as a percentage of the wet salicylate-free tissue, is almost unchanged. The retention of salicylate up to as much as 40 per cent. of the initial dry weight, even after prolonged washing in distilled water, is noteworthy. The lowering effect of salicylate treatment on the  $T_s$



is, however, not to be attributed to this presence of salicylate, since equally low shrink temperatures are obtained after almost complete removal of the salicylate by weak bicarbonate (Table VIII).

The apparent lack of effect of pretreatment with  $\text{CaCl}_2$  on the Ts (Table VI) contrasts with the known lyotropic effect of this salt on hide powder (Gustavson, 1956c). Here again the difference is probably attributable to the denaturation which the collagen has undergone in the production of hide powder.

Further evidence favouring the presence of two distinct types of stabilizing bonds in the collagen molecule may be deduced from the behaviour of acid soluble collagen in salicylate. Since acid soluble collagen has  $\text{Ts}_2$  of only  $45^\circ \text{C}$ ., it may be inferred from what we have said before that the bonding is entirely of the hydrogen type. The complete solubility of this form of collagen in salicylate is in conformity with this view. Failure to reprecipitate such a solution of acid soluble collagen by dialysis and alkalization shows further that the disruption of the hydrogen bonds brought about by the salicylate is irreversible.

**Shrinkage Temperature in Salicylate Solutions.**—The Ts undergoes much greater reduction when carried out in the presence of salicylate (Fig. 2) than when treated for 4 days in the same solution and thoroughly washed before determining the Ts in saline. Still more remarkable is the effect of the presence of relatively low concentrations of salicylate on the  $\text{Ts}_2$ , which, it will be recalled, is scarcely affected by pretreatment with high concentrations of salicylate when the Ts is subsequently determined in saline. It is difficult to explain these results, but they suggest that the bonds responsible for the stability at higher temperatures only become accessible to the salicylate molecules when the structure of the collagen fibrils is itself disorganized by the steric changes that underline the shrinkage occurring at lower temperatures. This is borne out by the remarkable coincidence of the two curves showing the relationship of  $\text{Ts}_2$  to molarity of salicylate when the determination is made after 5 days or immediately. The inference from this coincidence is that the bonds responsible for stability at the higher temperature remain intact during the whole 5 days of immersion and only become affected during the process of shrinkage in the presence of salicylates.

**Effect of Salicylate on Tryptic Digestibility.**—The tryptic digestibility of both collagen and non-collagen protein is affected by exposure to salicylate, whereas only about half the non-collagen protein originally present is digestible by trypsin without

salicylate pretreatment. 1 M salicylate for 4 days renders the whole of the non-collagen protein trypsin digestible, although the collagen itself still remains almost completely resistant. The resistance of native collagen to tryptic digestion is unlikely, therefore, to be due to the presence of a non-collagenous protein-cementing substance. Treatment with 2 M salicylate results in about half of the collagen becoming digestible by trypsin. Determination of the Ts of the residue shows, however, that it is not the whole of the fraction with low Ts that is digested, since the Ts is virtually unchanged. That hydrogen bond breakers alone can render native collagen, at least in part, digestible by tryptic enzymes suggests a possible mechanism by which mature collagen fibres might be removed *in vivo*, under both physiological and pathological conditions.

**Variation with Age of Shrinkage Temperature and of the Response of Ts to Salicylate.**—Native collagen, at least as judged by its Ts, is in its least stable form during foetal life. Increasing stability, as shown by the rising Ts with age (Table IX), could be attributed either to an increase in number of hydrogen bonds, or to the development of other types of internal bonding. Failure to reduce the  $\text{Ts}_1$  of mature adult tissue by immersion in salicylate to the level obtainable with foetal tissue, suggests that the bonds responsible for the increased stability at the later age are not hydrogen bonds. As we have pointed out above, however, a similar result would be obtained if the extra hydrogen bonds were inaccessible to the salicylate. The results obtained when shrinkage is determined in the presence of salicylate, the  $\text{Ts}_1$  in these circumstances falling to the same level as that of foetal tissue, does suggest that the bonds affected are indeed hydrogen bonds, but less accessible than those present in young unshrunk tissue. A possible way by which such extra hydrogen bonds could arise is between the sites occupied by mucopolysaccharides, as these are progressively lost with increasing age. The evidence provided by x-ray diffraction (Hartmann, Gattow, and Fricke, 1957) of increasing orientation of collagen with increasing age is compatible with this view. The apparent break in the curve showing rise of Ts with age between the ages of 15 and 44 years corresponds roughly with the period of active sex life. The relationship of this to hormonal control needs no emphasis.

**Shrinkage Temperature of Uterine Collagen.**—The anomalous position of uterine collagen is presumably related to its cyclic activity and this is in part confirmed by the rise in  $\text{Ts}_1$  which follows

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the menopause. The speed with which large quantities of collagen disappear in the puerperal uterus makes it a subject of special interest, since it contrasts so markedly with the stability of adult collagen elsewhere. Although we have not found it any more readily digestible by trypsin than other native collagen, its initially lower  $T_s$  must render it more sensitive to the mechanisms *in vivo* which are presumably available to solubilize and remove unwanted collagen.

**Fluorescence of Collagen.**—It is well known that collagen fluoresces in ultra-violet light. Of the specimens of mammalian collagen which we have examined, the only two tissues which failed to give this fluorescence were pre-menopausal uterine and foetal collagen. The acquisition of the adult type of fluorescence seems to appear in non-uterine collagen sometime between the ages of 11 months and 4 years. In the uterus the appearance of similar fluorescence occurs approximately at the menopause. The nature of the fluorescent material and its significance are still obscure.

**Shrinkage Temperature of Collagen from Rheumatoid Nodules.**—Histological study of rheumatoid nodules shows evidence of fragmentation, fibrillation, and disappearance of collagen (Glynn and Reading, 1956), which is supported by more modern methods of examination (Kellgren, 1952). This loss of collagen must be the result of enzymatic activity and, at the pH obtaining in the tissues, the only known proteolytic enzymes available are tryptic in type, to which, as we know, unaltered collagen is highly resistant. This of necessity implies that, before its removal by such enzymes, the collagen must undergo some fundamental change which could most readily be detected as a fall in  $T_s$ . This, as we have shown in the experimental section of this paper, can be detected by the use of a micro-method. From what is known of the structure of collagen which renders it resistant to tryptic enzymes, it is apparent that some fundamental change in the internal structure is essential as a preliminary to enzymatic removal. This could conceivably be brought about by local concentrations of substances capable of disrupting the hydrogen bonds.

### Summary

(1) The shrinkage temperature and digestibility by trypsin of human and animal collagen were studied before and after various treatments.

(2) Periodate and hyaluronidase had no greater effect on the shrink temperature than did the buffers in which the treatment was given. Acetate buffer at pH 4.0 or N/5 KOH lowered the shrink tempera-

ture, but citrate and phosphate buffers at pH 4.0 and 7.0 respectively were without effect.

(3) When tissues were treated with hydrogen bond breakers and then washed, there was a considerable lowering of shrink temperature. This effect was greater when shrinkage was determined in solutions of hydrogen bond breakers. Of the reagents tested, hydrogen donors were more effective than hydrogen acceptors; salicylates caused the greatest lowering. The reduction in shrink temperature was shown to be independent of any induced swelling.

(4) Pretreatment with 1 M salicylate followed by trypsin removed virtually all the non-collagen protein but very little of the collagen. With 2 M salicylate followed by trypsin, nearly half the collagen was digested. No collagen was extracted by the salicylate alone.

(5) Human collagen from older subjects had a significantly higher shrink temperature than that from younger subjects, but foetal collagen showed no such variation with foetal age.

(6) Uterine collagen had a shrink temperature similar to that of foetal or very young collagen.

(7) Collagen usually fluoresces strongly in ultra-violet light. Foetal collagen and pre-menopausal uterine collagen do not fluoresce, but uterine collagen acquires fluorescence after the menopause.

(8) Collagen from three rheumatoid nodules fluoresced poorly in ultra-violet light. The shrinkage temperature was distinctly lower than that of normal collagen.

(9) The factors responsible for stabilizing collagen are discussed together with some biological implications.

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### Observations sur la température de contraction du collagène et ses variations selon l'âge et la maladie

#### RÉSUMÉ

(1) On a étudié la température de contraction et la digestibilité par la trypsine du collagène humain et animal avant et après certains traitements.

(2) L'effet du périodate et de l'hialuronidase sur la température de contraction n'était pas supérieur à celui des tampons usés dans le traitement. Le tampon d'acétate au pH 4.0 ou KOH à N/5 faisait baisser la température de contraction, mais les tampons de citrate et de phosphate au pH 4.0 et 7.0 respectivement n'avaient aucun effet.

(3) Quand on traitait les tissus par des briseurs de liaison hydrogénés et on les lavait, il s'y produisait une baisse considérable de la température de contraction. Cet effet était plus accentué lorsqu'on déterminait la contraction dans des solutions de briseurs de liaison hydrogénés. Parmi les réactifs essayés, les donneurs d'hydrogène étaient plus efficaces que les récepteurs d'hydrogène; les salicylates provoquaient la baisse la plus accentuée. La réduction de la température de contraction était indépendante de tout gonflement provoqué.

(4) Le traitement préalable par le salicylate 1M, suivi de trypsine, enlevait virtuellement toute la protéine non-collagène, mais très peu de collagène. Avec la salicylate 2M, suivi de trypsine, presque tout le collagène se trouvait digéré. On ne pouvait pas extraire du collagène avec le salicylate seul.

(5) Le collagène humain des sujets âgés avait une température de contraction appréciablement plus élevée que celui des sujets plus jeunes, mais le collagène foetal n'accusait pas de telles variations selon l'âge foetal.

(6) La température de contraction du collagène utérin était similaire à celle du collagène foetal ou très jeune.

(7) Le collagène est généralement fluorescent à la lumière ultra-violette. Le collagène foetal et utérin pré-ménopausique ne l'est pas, mais le collagène utérin devient fluorescent après la ménopause.

(8) La fluorescence à la lumière ultra-violette du collagène provenant de nodules rhumatismaux est faible;

sa température de contraction est nettement inférieure à celle du collagène normal.

(9) On discute les facteurs intervenant dans la stabilisation du collagène ainsi que les implications biologiques.

### Observaciones sobre la temperatura de contracción del colágeno y sus variaciones según la edad y la enfermedad

#### SUMARIO

(1) Se estudió la temperatura de contracción y la digestibilidad por la tripsina del colágeno humano y animal antes y después de ciertos tratamientos.

(2) El efecto del periodato y de la hialuronidasa sobre la temperatura de contracción no fué superior al de los tapones empleados en el tratamiento. El tapón de acetato al pH 4.0 o KOH N/5 hacía bajar la temperatura de contracción, pero los tapones de citrato y de fosfato al pH 4 y 7 respectivamente no tuvieron efecto alguno.

(3) Cuando se trataba los tejidos con quebradores hidrogenados de lazos y se los lavaba, se obtenía una baja considerable de la temperatura de contracción. Este efecto fué más marcado al determinar la contracción en soluciones de quebradores hidrogenados de lazos. Entre los reactivos empleados, los dadores de hidrógeno fueron más eficaces que los aceptadores de hidrógeno; los salicilatos provocaban la baja la más acentuada. La reducción de la temperatura de contracción fué independiente de toda tumefacción provocada.

(4) El tratamiento previo con el salicilato 1M, seguido de tripsina, eliminaba virtualmente toda la proteína non-colágena, pero muy poco de colágeno. Con el salicilato 2M, seguido de tripsina, casi todo el colágeno se veía digerido. No se pudo extraer colágeno alguno con el salicilato solo.

(5) La temperatura de contracción del colágeno humano de sujetos de edad avanzada fué apreciadamente mayor que la de sujetos jóvenes, pero no hubo tales variaciones según la edad en el colágeno fetal.

(6) La temperatura de contracción del colágeno uterino fué similar a la del colágeno fetal o muy joven.

(7) El colágeno es generalmente fluorescente a la luz ultra-violeta. El colágeno fetal y uterino premenopáusico no lo es, pero el colágeno uterino se vuelve fluorescente después de la menopausia.

(8) La fluorescencia a la luz ultra-violeta del colágeno de los nódulos reumáticos es muy débil. La temperatura de contracción es marcadamente más baja que la del colágeno normal.

(9) Se discuten los factores interviniendo en la estabilización de colágeno así como las implicaciones biológicas.



CLINICAL FEATURES AND COURSE OF ANKYLOSING SPONDYLITIS

AS SEEN IN A FOLLOW-UP OF 222 HOSPITAL REFERRED CASES

BY

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Despite the increasing recognition of ankylosing spondylitis, particularly as a result of two world wars, there is little information relating to the course of this disease on which to base prognosis. While there are many studies dealing with the clinical manifestations, to date only Blumberg and Ragan (1956) have attempted to study the physical condition and functional ability of patients many years after the onset of ankylosing spondylitis, and even here the value of the study was diminished because of inability to trace approximately half the patients. The present study details a more complete follow-up of a group of spondylitics seen and treated at one hospital over 16 years. Although primarily concerned with the follow-up results, various aspects of the clinical picture have been studied and where these are of interest they will be presented.

Patients Studied

During the period January, 1940, to December, 1955, 242 patients were diagnosed at the Hammersmith Hospital as suffering from ankylosing spondylitis. Approximately two-thirds of these patients had been referred to the radiotherapy department from outlying hospitals and most of the others had attended the out-patient clinic for rheumatic diseases.

While no claim can be made for a hospital-referred group to represent the true spondylitic population, the latter has never been defined, and the hospital-referred group remains the one about which it is desirable to know the outcome, whether the disease be treated or untreated. Since early cases demand radiography for diagnosis, the hospital-referred group corresponds perhaps more closely than in other categories of disease to the diagnosable entity, apart from special population surveys.

During 1955 and 1956 an attempt was made to trace all these patients and, wherever possible, they were interviewed and examined. Where personal examinations were not possible, reports were obtained on the patients' physical state following attendances at other

hospitals, and in a few cases patients were asked to complete a questionnaire.

Of the original 242 patients, twenty were excluded from further study, seven because of inadequate initial information or radiographs, seven because of incorrect diagnoses, and six because there were only minimal or doubtful changes in the sacro-iliac joint x rays and no physical signs to support a diagnosis of ankylosing spondylitis. Follow-up details of the remaining 222 patients are shown in Table I. Only ten of these patients could not be traced, and seventeen had died during the follow-up period.

TABLE I  
FOLLOW-UP DETAILS OF 222 PATIENTS WITH ANKYLOSING SPONDYLITIS

No. of Patients	Sex		Type of Follow-up
	Male	Female	
17	16	1	Known to be dead
142	122	20	Seen personally at follow-up
33	26	7	Follow-up by proxy at another hospital
20	9	11	Postal follow-up
10	8	2	Follow-up unsuccessful
222	181	41	Totals

All 222 patients fulfilled the following criteria:

- (1) All had a clinical picture compatible with the diagnosis of ankylosing spondylitis, the minimal requirement being backache.
- (2) All showed radiological changes in both sacro-iliac joints. In a few cases only x-ray reports were available, but in these appropriate changes in the sacro-iliac joints were described and the patients themselves showed advanced changes of ankylosing spondylitis.

Most of the patients had received a variety of treatments including radiotherapy. We have made no detailed attempt to relate treatment to course since there is no evidence showing significant beneficial effects over a prolonged period of any particular type of treatment. We have been concerned with the long-term course and state of a patient with this disease treated



by the methods usually advocated over the last 16 years in Great Britain.

Apart from the information obtained at follow-up visits, most of these patients had been seen intermittently at Hammersmith Hospital over periods varying from 1 to 20 years (mean follow-up 4.6 years), and considerable information was available from the case records.

Analysis of the cases when first seen (Table II) showed that the type of case referred to hospital during the period studied did not vary significantly, except in one respect. Those patients seen during the years 1951 to 1955 showed a significantly better functional status when first seen than did the earlier patients. The large increase in the number of cases seen during 1951 to 1955 was due to the closing down of a nearby radiotherapy centre and consequent transfer of its patients in 1950.

TABLE II  
CLINICAL FEATURES

Clinical Features of 222 Spondylitics When First Seen		Year		
		1940-45	1946-50	1951-55
Total Patients Seen		28	61	133
Percentage of Females		11	20	20
Average Age (yrs)		35.0	38.9	38.2
Percentage Type of Onset		67	82	82
	nal	33	18	18
		41	41	36
Percentage Duration of Disease (yrs)	0-10	33	28	30
	Over 10	26	31	34
Previous Radiotherapy (per cent.)		11	16	18
Percentage Functional State	Working (Grade 5 and 4)	57	56	74*
	Unable to Work but Mobile (Grade 3)	11	18	13
	Chairbound or Bedridden (Grade 2 and 1)	32	26	13
	Mean Functional Grade	3.4	3.4	3.9

\* Difference significant at 5 per cent. level.

Significance has been assessed by the use of the  $\chi^2$  test, using Yates' modification where appropriate.

#### Clinical Features at Onset

**Sex Incidence and Age at Onset.**—Table III shows the sex ratio and distribution of ages at which initial symptoms were noted. The sex ratio for the whole series was 4.4 males to 1 female. Because of the occasional history of episodes of peripheral arthritis or arthralgia often diagnosed as rheumatic fever, such an episode was accepted as marking the onset of the spondylitis only when there were permanent residua or when the peripheral joint symptoms merged into the spinal symptoms.

TABLE III  
SEX INCIDENCE AND AGE AT WHICH INITIAL SYMPTOMS WERE NOTICED IN 222 PATIENTS WITH ANKYLOSING SPONDYLITIS

Age at Onset (yrs)	No. of Patients	Sex		Percentage Total Cases in each Decade	
		Male	Female	Male	Female
10-19	40	30	10	16.6	24.4
20-29	101	87	14	48.1	34.1
30-39	56	48	8	26.5	19.5
40-49	20	13	7	8.8	22.0
50 and Over	5	3	2		
Total	222	181	41	100	100

70 per cent. of the patients had first noticed symptoms between the ages of 20 and 40 years and, though five patients remembered no disability before the sixth decade, physical and radiological evidence at the time of the first examination suggested that the disease had in fact begun before the age of 50 years. While the initial symptoms in males occurred mainly in the third and fourth decades, the onset in females was spread more evenly over five decades, the difference being significant at the 5 per cent. level.

The earliest age at onset was 11 years (Case 1):

**Case 1, a male accountant aged 36 in 1955**, had first noticed jabbing pains in both buttocks radiating down to the mid-thighs at the age of 11; the pains occurred in bouts lasting several months, but did not incapacitate him and at the age of 21 he joined the Royal Air Force. The work was mainly clerical but 3 years later, 13 years after the initial symptoms, he was discharged with a diagnosis of ankylosing spondylitis. Radiotherapy to the lower spine relieved all pain but had to be repeated for an exacerbation in the cervical spine 3 years later. At the age of 33 years bilateral pulmonary tuberculosis was diagnosed. When last seen in 1955 the patient had a rigid spine and a normal sedimentation rate.

**Heredity.**—Table IV shows the frequency of rheumatic complaints in the families of these

TABLE IV  
FAMILY HISTORY OF 222 PATIENTS WITH ANKYLOSING SPONDYLITIS

Relatives' Status	No. of Patients	Sex		No. of Relatives Affected
		Male	Female	
Hospital Diagnosis of Ankylosing Spondylitis	14	10	4	17
Ankylosing Spondylitis not Diagnosed but Description Suggestive	11	11	0	11
Hospital Diagnosis of Rheumatoid Arthritis	5	3	2	7
Rheumatoid Arthritis not Diagnosed but Description Suggestive	3	3	0	4

patients; 6 per cent. had relatives with definite ankylosing spondylitis and a further 5 per cent. had relatives probably suffering from this condition. With one exception (a nephew) the affected relatives were parents, siblings, or offspring. No enumeration of the total relatives at risk was made.

**Site of Onset.**—Table V shows the site of initial symptoms. Although eighteen patients had an onset diagnosed as sciatica, re-examination of their symptoms suggested that in fourteen the pain was really sacro-iliac in origin, i.e. aching pain in the lower buttocks radiating only into the upper thighs, frequently bilateral and recurring over months or years. One further patient described what was clearly pain originating from the hip joint (pain radiating down the lateral thigh to the knee, worse on hip movement and weight bearing, and associated with radiological changes in the corresponding hip joint). Only three patients described a pain that was of sciatic distribution, but unfortunately were not seen at this early stage. Although sciatica has been claimed to herald the onset of ankylosing spondylitis in about 10 per cent. of patients (Polley and Slocumb, 1947), pain of typical sciatic distribution (radiating down the posterior thigh and calf into the foot) is unusual.

19 per cent. of all patients had an extraspinal onset (initial symptoms in the hips, shoulders, peripheral joints, or heels), and a further 2 per cent. first presented with uveitis.

TABLE V  
SITE OF INITIAL SYMPTOMS IN 222 PATIENTS WITH ANKYLOSING SPONDYLITIS

Site	No. of Patients	Sex	
		Male	Female
Sacro-iliac joints .. ..	90	70	20
Lumbar spine .. ..	53	41	12
Thoracic spine .. ..	12	9	3
Cervical spine .. ..	9	6	3
Sciatica* .. ..	3 (18)*	3	0 (16/2)*
Whole spine .. ..	1	1	0
Root joints .. ..	12	12	0
Peripheral joints .. ..	29	27	2
Heels .. ..	2	2	0
Iris (iritis) .. ..	6	6	0
Not stated .. ..	5	4	1
Totals .. ..	222	181	41

\* Although the initial symptom was recorded as sciatica in eighteen patients, the description of the pain in fifteen suggested sacro-iliac or hip-joint pain and is entered as such.

**Type of Onset.**—165 patients (74 per cent.) described a gradual onset, and 45 patients (20 per cent.) an acute onset of symptoms. In eleven patients the type of onset was not recorded. One patient presented a picture of palindromic rheumatism for

30 years before the spondylitis was recognized (Case 2):

**Case 2, a male scientist aged 55 in 1956,** had suffered from attacks of synovitis at intervals of 2 or 3 years since the age of 22; initially the pain was in the right ankle and later in the knees. Between attacks he suffered only slight morning stiffness of the knees. These attacks were thought to be allergic. At the age of 51 years he first noticed pains in the chest and thoracic spine and at this time there was limitation of spinal movement and radiographs showed ankylosis of the sacro-iliac joints. Differential agglutination and erythrocyte sedimentation tests were normal. Radiotherapy gave symptomatic relief in both the spine and the knees.

Most patients with a spinal onset noticed definite aggravation of the pain after resting, pain and stiffness being most marked on rising from bed and again after reclining in an armchair in the evening. Many found relief after activity, and a few found it necessary to get out of bed during the night to "limber up" before completing their night's rest. Many, including some with quiescent disease, found that their pain was aggravated by heavy exertion or by jolting the spine.

Follow-up

The following account is based upon a study of the 212 patients whose follow-up was successful. It seems unlikely that the omission of the ten cases (eight male, two female) whose follow-up was unsuccessful, will introduce serious errors into the conclusions.

**Deaths.**—Seventeen patients (sixteen male and one female) are known to be dead; the causes of death are listed in Table VI (overleaf). In none was the arthritis a direct cause, but in one it was contributory (severe kyphosis with dysphagia due to a displaced aorta compressing the oesophagus), and three patients died of probable complications of the radiotherapy (leukaemia and pulmonary tuberculosis activated by deep x ray).

**Sites Involved in the Course of the Disease.**—Table VII (overleaf) shows the frequency with which various joints were involved in the course of the disease; for this study an involved joint was defined as any joint causing symptoms with either physical signs observed at hospital or radiological changes. This definition will apply throughout this paper.

(1) **Sacro-iliac Joints.**—Because of our criteria for inclusion, all patients showed bilateral sacro-iliac changes. While occasional cases of ankylosing spondylitis without initial sacro-iliac changes have been reported (Forestier, 1939; Oppenheimer, 1943; Hart, Robinson, Allchin, and MacLagan, 1949), such

TABLE VI  
CAUSES OF DEATH IN SEVENTEEN PATIENTS WITH ANKYLOSING SPONDYLITIS

Period of First Attending Hospital	Patient	Sex	Age at Death (yrs)	Duration of Spondylitis at Death (yrs)	Cause of Death
1940-45	A.O.	M	57	30	*Malignant tumour(?) of pleural origin
	W.A.	M	62	29	*Hodgkin's disease
	S.C.	M	69	28	*Dysphagia from compression of oesophagus by aorta Inhalation pneumonia
	J.R.	M	55	26	Street accident
	M.B.	F	37	23	*Bronchiectasis and cor pulmonale
	P.W.K.	M	42	9	Not known
	C.H.	M	56	8	*Post-operative cerebral embolism
1946-50	J.E.K.	M	54	?	*Fracture dislocation of spine
	S.L.	M	48	32	*Chronic bronchitis and cor pulmonale
	W.J.	M	43	15	*Myeloid leukaemia
	G.J.	M	38	12	Pulmonary tuberculosis
	L.D.	M	53	12	Pulmonary tuberculosis
	S.W.	M	57	8	*Myocardial infarct
1951-55	G.P.	M	35	6	Pulmonary tuberculosis
	A.E.	M	69	53	*Carcinoma of pancreas
	J.B.	M	61	37	Myocardial infarct
	A.R.	M	57	22	Carcinoma of stomach

\* Indicates that a *post-mortem* examination was obtained.

TABLE VII  
BONE AND JOINT LESIONS FOUND DURING FOLLOW-UP  
IN 212 PATIENTS WITH ANKYLOSING SPONDYLITIS

Site of Lesions	Total No. of Patients	Sex	
		Male	Female
Sacro-iliac joints .. .. .	212	173	39
Lumbar spine .. .. .	186	152	34
Thoracic spine .. .. .	156	125	31
Cervical spine .. .. .	110	92	18
Hips .. .. .	71	63	8
Knees .. .. .	34	29	5
Ankles .. .. .	15	12	3
Feet .. .. .	24	21	3
Shoulders .. .. .	35	30	5
Elbows .. .. .	12	9	3
Wrists .. .. .	10	8	2
Hands .. .. .	14	11	3
Manubrio-sternal joints .. .. .	10	8	2
Sterno-clavicular joints .. .. .	4	4	0
Acromio-clavicular joints .. .. .	4	4	0
Temporo-mandibular joints .. .. .	1	1	0
Costo-vertebral joints .. .. .	47	40	7
Bony spurs or erosions .. .. .	52	45	7
Pubic symphysis .. .. .	43	38	5
Heels .. .. .	5	4	1

cases must be rare and difficult to diagnose with confidence until sacro-iliac changes become manifest. In our experience, early changes in the sacro-iliac

joints are better shown by the anteroposterior view than by oblique views. Indeed, the latter may prove misleading, for seven of the present cases showed no abnormality on oblique views at a time when changes were suspected on the anteroposterior view (Fig. 1, opposite).

The subsequent course and radiographs confirmed the diagnosis in all seven cases. In doubtful cases, Romanus and Ydén (1955) found the postero-anterior view of value.

(2) *Spinal Involvement.*—The extent of spinal involvement is greater in those with long-lasting disease (Table VIII, opposite).

The thoracic and lumbar spine shows the same trend with duration of disease as the cervical spine. At follow-up, in only sixteen patients, mostly cases of relatively short duration (mean 6.2 years, standard deviation 3.8 years), was the disease confined to the sacro-iliac joints.

Although the disease seems to spread up the spine, we have observed, as have other writers (Borak, 1946), that the vertebral erosions (or “anterior



Fig. 1.—Ankylosing spondylitis of 4 months' duration. Antero-posterior view of sacro-iliac joints (a) shows loss of definition of articular margins and erosions, especially on the left side. Oblique views (b and c) were then normal but showed erosions at a later stage.

TABLE VIII

FREQUENCY OF SPINAL, ROOT JOINT, AND PERIPHERAL JOINT INVOLVEMENT AT LAST EXAMINATION CORRELATED WITH DURATION OF SYMPTOMS IN 211\* PATIENTS WITH ANKYLOSING SPONDYLITIS, FOLLOWED UP UNTIL DEATH OR TO THE PRESENT TIME

Total Duration of Symptoms (yrs)	Total No. of Patients in Each Group	Percentage of Patients in Each Group with Involvement of:				
		Cervical Spine	Thoracic Spine	Lumbar Spine	"Root" Joints	Peripheral Joints
1-5	30	27	57	70	27	17
6-10	53	42	57	81	40	28
11-15	54	50	80	91	41	13
16-20	27	74	92	100	41	30
Over 20	47	68	96	94	45	36

\* In one further patient, omitted from this Table, the duration of symptoms was not known.

spondylitis" of Romanus and Ydén, 1955) and the disk ossification usually make their first appearance in the lower thoracic and upper lumbar spine (Fig. 2, overleaf). Although anterior spondylitis was observed infrequently (23 per cent. of those with x rays available for review), this was probably because many patients were spondylitics of long standing and radiographs of early lesions were not always available.

In some cases anterior spondylitis was seen in the cervical region, and one case (A.H.) is of outstanding interest since the upper five cervical vertebrae were fused as well as the lowest ones (Fig. 3, overleaf). Movement could therefore only take place to a very limited extent at C 6-7 and this is where the anterior erosion occurred. The fusion always seems to be associated with sclerosis and it may possibly be an aseptic pressure-necrosis of bone. It is worth noting that, in the spine, disk degeneration may

occur before ossification of the disk edge and ligaments, giving an x-ray appearance of osteophytosis affecting one or more vertebrae (Fig. 4, overleaf).

The costovertebral joints were radiologically involved in 47 patients and two of these showed ossification of the capsules of the first costovertebral joints (Fig. 5, overleaf).

(3) "Root Joint" Involvement.—This is taken to mean involvement of the hips or shoulders. 83 (39 per cent.) of the patients showed involvement of either or both of these joints. Rather surprisingly there was little greater incidence of root joint involvement in cases seen after the first 10 years of spondylitic symptoms (Table VIII). 50 per cent. of those patients in whom the disease began before the age of 20 years showed root joint involvement compared with 36 per cent. of those with a later onset. However, this difference does not quite reach significant levels.



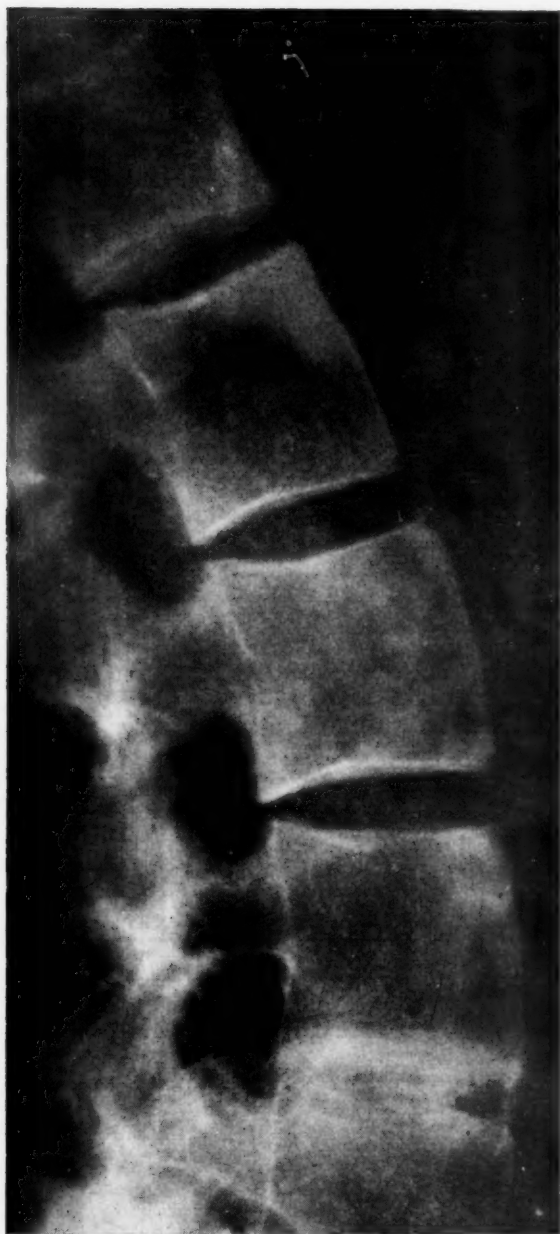


Fig. 2.—“Anterior spondylitis”. Erosions of anterior angles of vertebral bodies progressing to a stage of healing with sclerosis (adjoining top intervertebral disk), and still later to ossification in the disk edge (bottom intervertebral disk).

(4) *Peripheral Joints*.—Fifty patients (24 per cent.) showed involvement of the peripheral joints (excluding hips and shoulders) at some stage in the illness. Other writers have reported an incidence of peripheral joint involvement as high as 75 per cent. (Romanus and Ydén, 1955); this figure, however,



Fig. 3.—“Anterior spondylitis” in the cervical spine.

obviously depends upon the author's definition of “joint involvement”.

As with the root joints there was little change in the incidence of peripheral joint involvement in those who had had spondylitic symptoms for more than 10 years (Table VIII). The incidence of peripheral joint involvement in spondylitics with onset before the age of 20 years was 40 per cent. compared with 22 per cent. in those with an onset after that age. This difference is significant at the 5 per cent. level.

(5) *Extra-Articular Bone Lesions*.—Approximately one-quarter of the patients showed osteolytic lesions or what is presumably the healed stage of such lesions—areas of irregular cortical bone at one or more sites around the pelvis, upper femora, or feet (Table IX, opposite). The ischial tuberosities were the commonest sites for such lesions and, except in one case, these lesions were not seen at other sites

TABLE IX

FREQUENCY OF EXTRA-ARTICULAR BONE LESIONS  
FOUND DURING FOLLOW-UP IN 212 PATIENTS WITH  
ANKYLOSING SPONDYLITIS

Site		No. of Patients
Ischium	Left side only . . . .	12
	Greater on left . . . .	7
	Right side only . . . .	2
	Greater on right . . . .	4
	Bilateral and equal . . . .	25
Iliac crests . . . . .		14
Greater trochanter . . . . .		3
Lesser trochanter . . . . .		5
Heel . . . . .		5
Medial cuboid of foot . . . . .		1
Medial malleolus of tibia . . . . .		



Fig. 4.—Ankylosing spondylitis in a woman of 34 years. Intervertebral disk degeneration has preceded ossification, giving an appearance resembling osteophytosis of the lumbar spine. The sacro-iliac joints are eroded and sclerotic.



Fig. 5.—Ossification of capsule of first costotransverse joint in ankylosing spondylitis.



Fig. 6.—Erosion of ischial tuberosity and symphysis pubis in ankylosing spondylitis.

around the pelvis in the absence of ischial lesions. These erosions rarely occurred early in the course of the disease and were only occasionally of diagnostic help, *e.g.* in cases with doubtful x-ray changes, in the sacro-iliac joints. Since all these lesions lie close to tendon insertions it might be expected that they were due to abnormal strains at these sites, possibly because of the rigid spine. However, of the fifty patients with ischial tuberosity lesions, only 42 had an immobile or severely restricted thoraco-lumbar spine. Two patients with huge ischial erosions (Fig. 6) had only slight limitation of spinal movement, and three patients had none. One patient, a schoolboy, developed ischial erosions soon after a period of prolonged immobilization. Clearly, neither a rigid spine nor physical activity are essential for the production of ischial erosions. The predominance of ischial lesions on the left side was unexpected (Table IX).

Spurs of bone along the iliac crests and trochanters were often but not invariably associated with hip joint disease. The lesions behind and beneath the heels, though uncommon, were clinically and radiologically identical with those seen in patients with rheumatoid arthritis (Bywaters, 1954).

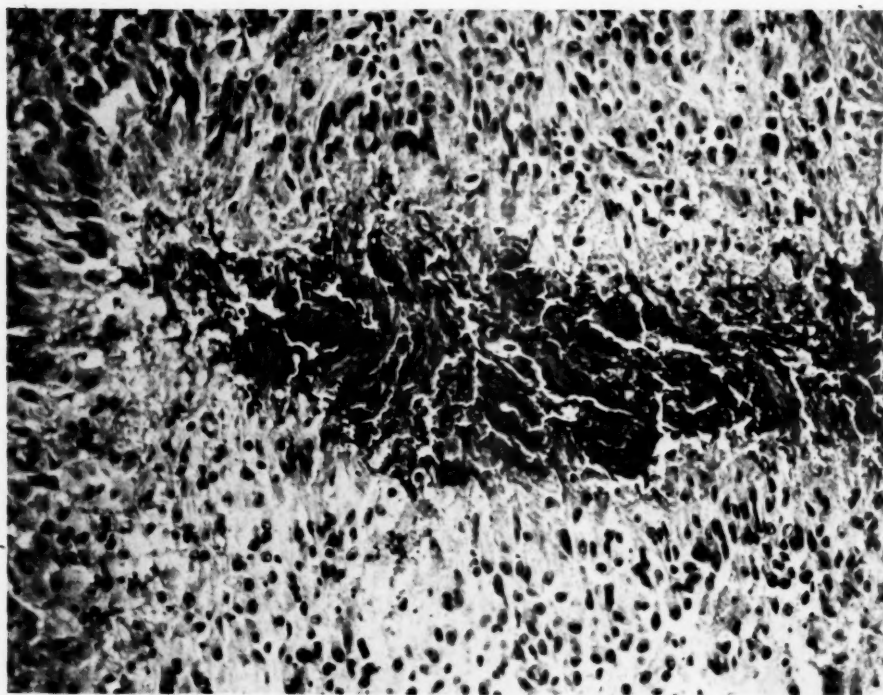


Fig. 7.—Subcutaneous nodule from a patient with ankylosing spondylitis and extensive peripheral arthritis. Haematoxylin and eosin  $\times 200$ .

(6) *Subcutaneous Nodules*.—One man with severe peripheral joint involvement (Case 3) developed multiple subcutaneous nodules identical clinically and histologically with those seen in rheumatoid arthritis (Fig. 7). This association has been reported once before (Smythe, 1956).

**Case 3**, an ex-lorry driver aged 69 in 1955, suffered an attack of "lumbago and sciatica" for one week at the age of 40 years, and then remained well until 7 years later when he complained of pain and stiffness in the neck. When aged 53 years he attended hospital and ankylosing spondylitis was diagnosed. The disease was then confined to the spine and root joints. Not until the age of 64 years did peripheral joint involvement occur and this progressed rapidly so that, at the time of his death at the age of 69, he showed severe deformity of all joints, including the fingers and toes; and multiple subcutaneous nodules. The sheep cell agglutination test was repeatedly negative. Radiographs and *post-mortem* examination confirmed the spondylitis and showed peripheral joint changes indistinguishable from those of rheumatoid arthritis. Necrobiotic nodules were also present in the pericardium.

One other patient showed a subcutaneous nodule but this was of the rheumatic fever variety and occurred during an attack of acute polyarthritis that was probably coincidental rheumatic fever:

**Case 4**, a male hairdresser aged 43 years in 1956, had suffered an attack of rheumatic fever lasting 3 months at the age of 11 years, and was thought to have had cardiac involvement. He then remained well until the age of 35 when a further attack of polyarthritis occurred

soon after a sore throat. When he was seen 3 months later only an apical systolic murmur was heard. Arthralgia continued with low back pain and stiffness, and after a further 3 months an x ray showed bilateral sacro-iliitis. The erythrocyte sedimentation rate (Westergren) was then 16 mm./hr. A subcutaneous nodule excised from over the sacrum was histologically typical of the rheumatic fever variety. When he was last seen in 1956, this patient had a rigid spine with only slight discomfort. The erythrocyte sedimentation rate and differential agglutination test then were normal.

**Functional State**.—On the basis of their working capacity and mobility at the time of follow-up, all the living patients were placed in one of five functional grades (Fig. 8, opposite), and this was correlated with the duration of symptoms. The slow decrease in functional capacity in the group with increasing duration of the disease is well shown, but it is interesting that 63 per cent. of the patients seen after more than 20 years of illness were working, admittedly in light occupations, and were supporting themselves and their families. After the same period only 12 per cent. of the patients were bedridden or chairbound, though even in this group a few strong-willed individuals did part-time work in the home or attended an office in a wheel chair. There was no evidence that females were any less disabled by the disease than were males.

**Employment**.—To some extent, the spondylitic may mask his functional deterioration by changing to a

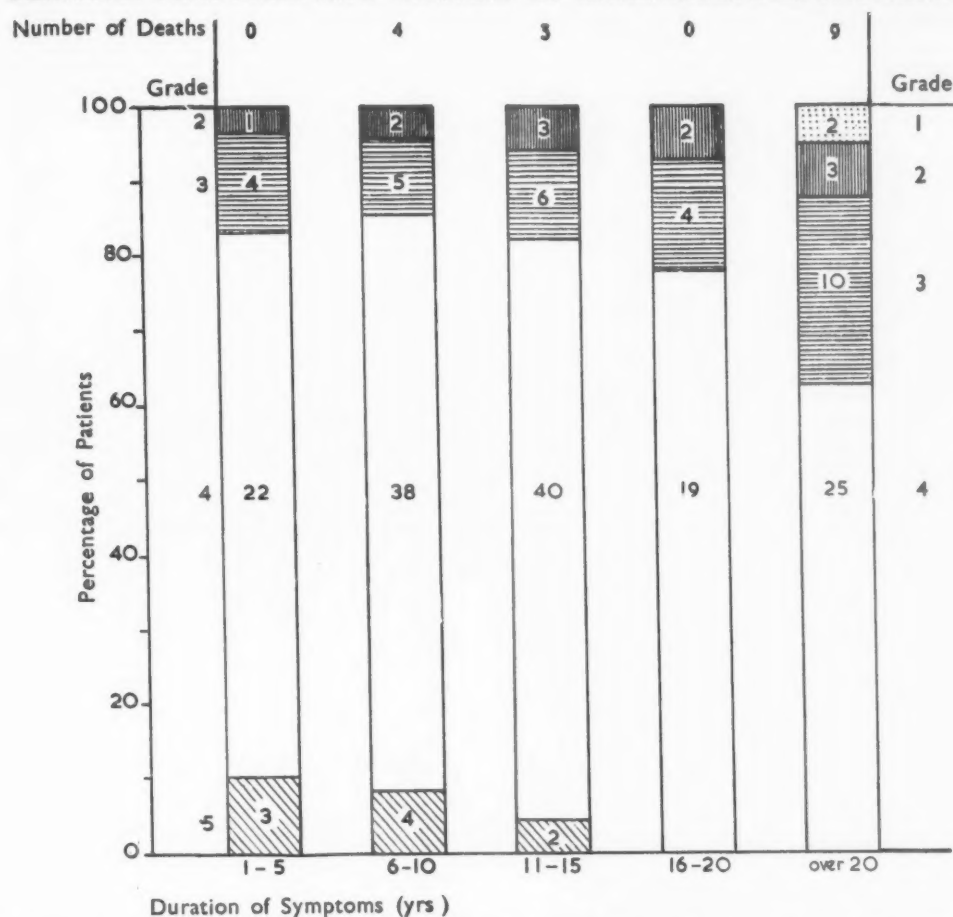


Fig. 8.—Functional status of 211 patients with ankylosing spondylitis of varying durations, graded in order of incapacity as follows:

- (5) Completely normal. Full-time work and physical recreations without symptoms.
- (4) Almost normal. Full-time work but symptoms after physical exertion.
- (3) Mobile but unable to work full time.
- (2) Chair-bound.
- (1) Bedridden.

Deaths are recorded above each column according to duration of symptoms at time of death. One death was omitted because the duration of illness was not known.

lighter occupation. Fig. 9 (overleaf) shows occupational data on the patients followed-up. After more than 20 years of spondylitic symptoms only 27 per cent. of forty patients were unemployed and a further 20 per cent. had changed or modified their employment because of the spondylitis. The apparent improvement in working capacity after 10 years of illness is probably not significant when one considers that nine of the seventeen deaths occurred in patients with spondylitis of greater than 20 years' duration.

**Deformity.**—Four grades of deformity were recognized (Fig. 10, overleaf). Here again there was a worsening in groups of longer duration.

Despite the few severely-deformed patients who continued to work, there was, as might be expected,

a correlation between functional capacity and deformity; 91 per cent. of the patients with no deformity were at work when last seen, whereas only 31 per cent. of the severely-deformed patients were working.

**Chest Expansion.**—A reduced chest expansion is an early and valuable sign of ankylosing spondylitis (Hart, Bogdanovitch, and Nichol, 1950). Of the patients who had had symptoms for 5 years or less, 81 per cent. had a chest expansion of 2 in. or less and 19 per cent. of less than 1 in. After more than 20 years of spondylitis, the corresponding figures were 96 and 62 per cent.

**Erythrocyte Sedimentation Rate.**—Opinions vary as to the value of the erythrocyte sedimentation rate as



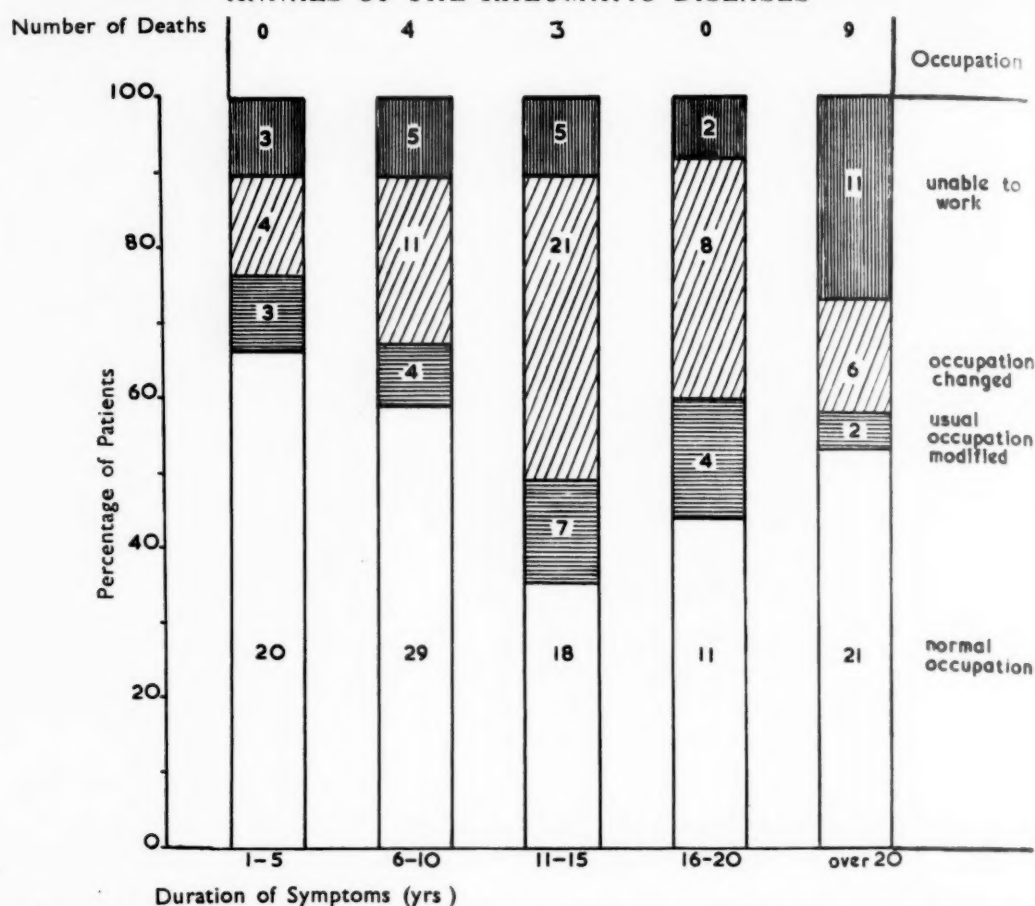


Fig. 9.—Occupational data on 211 patients with ankylosing spondylitis of varying durations. Deaths are shown above each column as in Fig. 8

an index of active disease in ankylosing spondylitis, but most agree that it is not invariably accelerated. It was estimated (by the Westergren method) at follow-up in 138 of the present patients, and was found to be 15 mm./hr or more in 64 patients (48 per cent. of those tested). This proportion did not vary significantly with the duration of symptoms for the series as a whole, nor did the mean rate differ significantly between the five duration groups (Table X).

TABLE X  
AVERAGE ERYTHROCYTE SEDIMENTATION RATE (WESTERGREN) FOR GROUPS OF PATIENTS WITH ANKYLOSING SPONDYLITIS OF VARYING DURATIONS

Total Duration of Symptoms (yrs)	No. of Patients Tested	Average E.S.R. (mm./hr)
1-5	19	26
6-10	33	20.2
11-15	34	22.5
16-20	26	23.2
Over 20	27	17.3

In individual cases, however, it fluctuated considerably during the course of the disease, usually in parallel with the clinical state and treatment (Fig. 11, opposite). This differs somewhat from the finding of Blumberg and Ragan (1956) that the "average" rate for a group of spondylitics is very high in the first 2 years of the illness, falling rapidly towards normal thereafter. This discrepancy may be due to the small number of spondylitics of very recent onset in the present series, and perhaps to the fact that peripheral joint involvement, with which the erythrocyte sedimentation rate is high, not infrequently brings the patient to hospital early in the course of his disease. In the present series, 28 well-documented patients had the erythrocyte sedimentation rate estimated early in their illness at the time of active peripheral joint disease, and the mean value was 65.2 mm./hr (standard deviation  $\pm 31.3$ ), which is considerably higher than that for the whole series. Indeed, it is exceptional to find a rate above 40 mm./hr at any stage if the disease is confined to the spine.

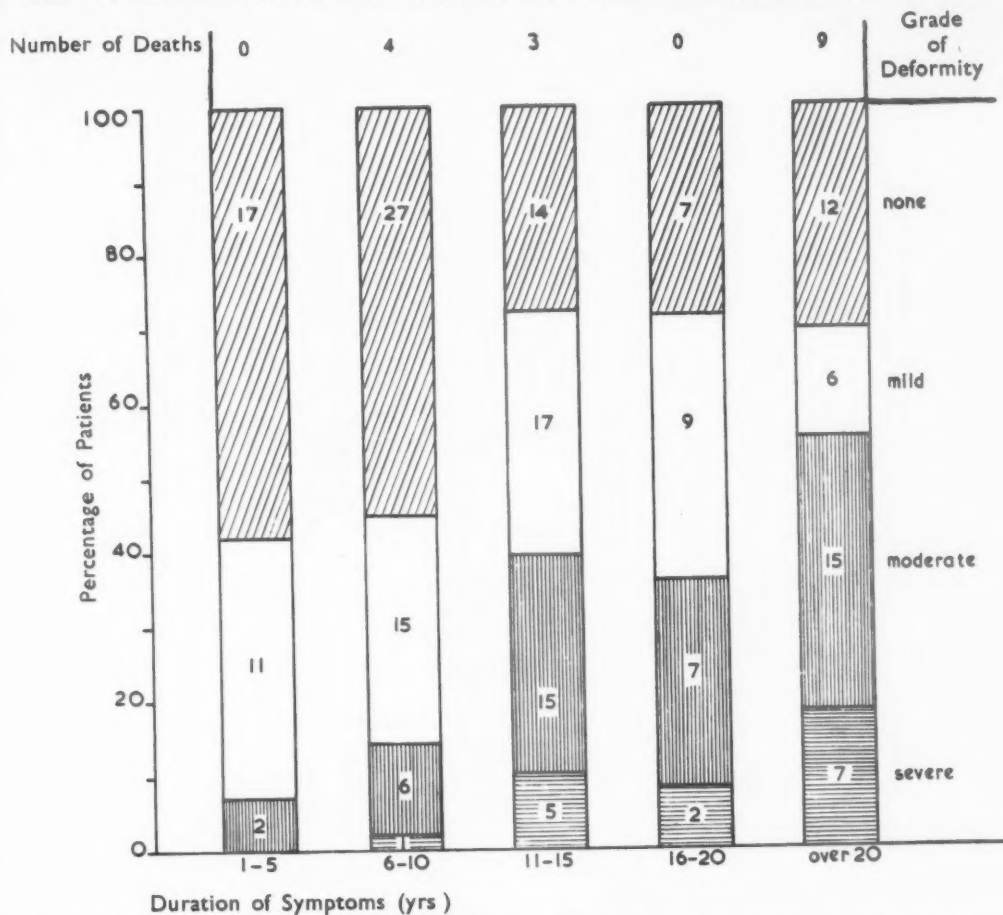


Fig. 10.—Deformity in 211 patients with ankylosing spondylitis of varying durations, graded in order of severity as follows:

- (4) None.
- (3) Mild. Slight kyphosis of thoracic and/or flattening of lumbar spine.
- (2) Moderate. Severe kyphosis or peripheral joint deformity but still mobile.
- (1) Severe. Grossly kyphotic spine and/or hip joint flexion deformity, sufficient to prevent ambulation.

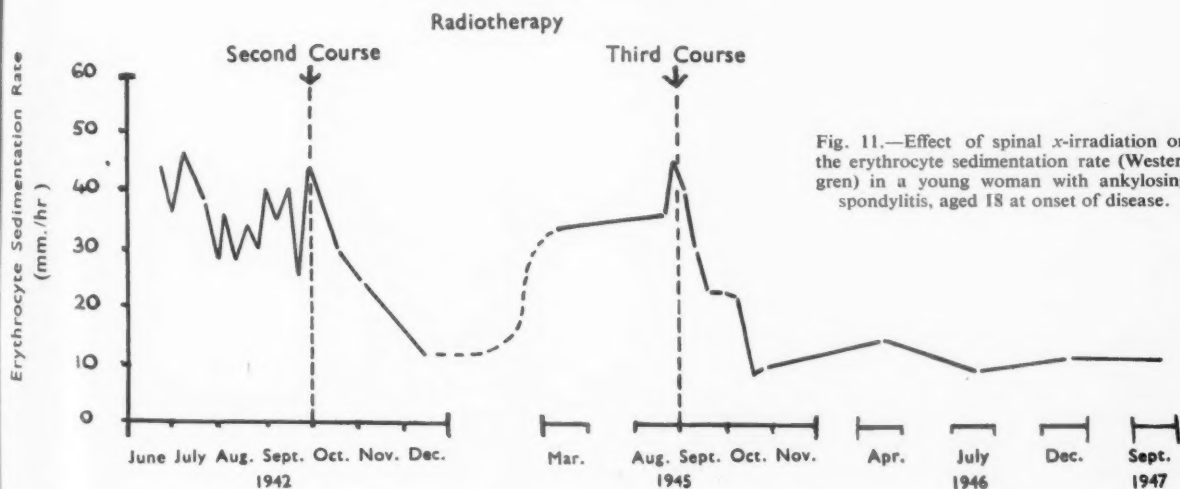


Fig. 11.—Effect of spinal x-irradiation on the erythrocyte sedimentation rate (Westergren) in a young woman with ankylosing spondylitis, aged 18 at onset of disease.

The 138 cases in which the rate was measured, were classified as active or inactive at follow-up on the basis of symptoms and/or changing physical and radiological signs. Of the 35 patients considered to have active disease, 29 (83 per cent.) had an abnormal rate (15 mm./hr or more), whereas sixty (58 per cent.) of 103 patients thought to have inactive spondylitis had a normal rate. Thus there was fair agreement between the clinical impression and the erythrocyte sedimentation rate in clearly active cases, but the agreement was much less satisfactory when the clinical impression suggested inactive spondylitis.

**Flocculation Tests.**—33 patients had various flocculation tests performed, usually including thymol turbidity, zinc sulphate turbidity, and colloidal gold tests, as well as a serum protein estimation. The results were normal except for three patients who showed hyperglobulinaemia and active spondylitis with peripheral joint involvement.

**Sheep Cell Agglutination Test.**—These were performed in 75 cases. In one (D.T.) male the titre was 1 : 32, but a repetition gave a negative result, and in another male (S.F.) it was 1 : 1,024 and had not been repeated. The latter patient had peripheral joint involvement but no subcutaneous nodules. In all other cases the result of this test was negative.

**Synovial Fluid.**—Synovial fluid from eight patients was examined and the changes found were similar to those associated with rheumatoid arthritis. The protein content ranged from 1.25 to 7.3 g. per cent. and the cell count from 3,300 to 23,000/c. mm. with a predominance of polymorphs in all except one case. Only one viscosity measurement was made and this was low.

**Radiotherapy.**—This was given to 200 patients and 91 of these received multiple courses. Though treatment was not standardized, most patients received total skin dosages ranging from 1,000 to 2,000r to each of four or five spinal fields. X rays were generated at 200 or 250 kV. with filters of 1 mm. copper and 1 mm. aluminium, and the focus-skin distance was 5 cm. Treatment was given over a period of approximately 3 weeks. The peripheral joints usually received considerably smaller dosages. The overall symptomatic results in the first 6 months after treatment are shown in Table XI.

Failure to respond to radiotherapy did not separate out a group of spondylitics with atypical features as suggested by Sharp and Easson (1954), but rather a group of patients with more extensive disease and particularly with peripheral joint involvement (Table XII). Radiotherapy to the root

TABLE XI  
RESULTS OF RADIOTHERAPY APPROXIMATELY  
6 MONTHS AFTER TREATMENT IN 200 PATIENTS  
WITH ANKYLOSING SPONDYLITIS

Relief of Pain	No. of Patients	Sex	
		Male	Female
Good. No residual complaints ..	134	112	22
Moderately or much improved but continuing to need analgesics ..	42	32	10
No benefit .. .. .	20	15	5
Not assessed .. .. .	4	4	0
Total .. .. .	200	163	37

and peripheral joints was certainly not as consistently beneficial as spinal irradiation. Of 51 patients given treatment to the root or peripheral joints, 27 obtained good relief of pain, twenty moderate relief, and four no relief. In 25 patients there was residual or even progressive limitation of joint movement after radiotherapy.

TABLE XII  
FACTORS AFFECTING RESPONSE TO RADIOTHERAPY  
IN 196 CASES OF ANKYLOSING SPONDYLITIS

Factors Investigated	Degree of Therapeutic Benefit					
	Good		Moderate		None	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
Lumbar spine involved	109	81	40	95	20	100
Thoracic spine involved	91	68	34	81	16	80
Cervical spine involved	48	36	30	70	14	70
Root joints involved ..	48	35	23	55	9	45
Peripheral joints involved	23	17	14	33	7	35
Iritis present .. .. .	37	27	5	12	8	40
Total No. of Cases ..	134		42		20	
No. in Each Category who had Multiple Courses ..	49	36	31	74	11	55
Mean Duration of Symptoms at Time of First X Ray ..		7.5		8		10.5

While of value in the relief of pain, radiotherapy rarely restores restricted movement (Desmarais, 1953), nor does it prevent further exacerbations. Table XIII (opposite) shows the proportion of patients developing further evidence of active disease after radiotherapy. As a measure of activity, all patients who suffered from further pain requiring analgesics for more than one month were considered to have relapsed. It was disappointing to find that only 43 per cent. of patients were not requiring regular analgesics within one year after treatment had been completed. Although many patients will em-

phatically state that pain is less after radiotherapy, a more objective means of assessment such as an analgesic consumption may be a better index of improvement. By 10 years after radiotherapy only 22 per cent. of the patients followed for that period could claim no further recourse to analgesic drugs. It should be emphasized that a number of these patients gained a further remission either spontaneously or after further radiotherapy.

TABLE XIII  
LONG-TERM RESULTS OF RADIOTHERAPY IN 183 PATIENTS WITH ANKYLOSING SPONDYLITIS  
The results apply to each patient's first course of therapy only.

Duration of Time since Therapy (yrs)	Percentage Pain-Free	No. of Patients in Group
1	42.6	183
2	36.4	173
3	33.1	142
4	27.6	123
5	26.3	99
10	21.8	78
Over 10	10	20

Complications of radiotherapy were infrequent and consisted of menstrual disturbances, which progressed to permanent amenorrhoea in six out of 19 patients, sterility and testicular atrophy in one patient, possible activation of pulmonary tuberculosis in two patients, and myeloid leukaemia in one patient. The last three patients eventually died.

Complications

(1) *Uveitis*.—56 patients (25 per cent.) gave a history of treatment for uveitis at an ophthalmic clinic or were found to have evidence of past uveitis, i.e. posterior synechiae. Seven of the patients with synechiae could remember no inflammation of the eyes. No band opacities were seen.

Although it has been reasonably claimed that the incidence of uveitis increases with the duration of follow-up (Hart and MacLagan, 1955), there was no evidence of this in the present series beyond the 10-year mark (Table XIV).

TABLE XIV  
INCIDENCE OF UVEITIS IN RELATION TO DURATION OF ANKYLOSING SPONDYLITIS IN 211\* CASES ADEQUATELY FOLLOWED UP

Duration of Symptoms (yrs)	No. of Patients in Each Group	Percentage of Patients with Uveitis
1-5	30	17
6-10	53	34
11-15	54	28
16-20	27	30
Over 20	47	26

\* One patient has been omitted because duration of illness was not known.

In most cases the uveitis was unilateral, often recurrent but sometimes involving each eye alternately. In four patients uveitis preceded other manifestations of spondylitis by 1 to 9 years. Uveitis first occurred in all adequately-documented cases within 10 years of the initial symptoms. There seemed to be no correlation between the attacks of uveitis and the activity of the spondylitis and four patients, whose arthritis had apparently been inactive for several years, continued to have attacks of uveitis.

Only two patients suffered serious visual impairment and one other required an iridectomy.

Uveitis occurred in 36 per cent. of those patients with peripheral joint lesions and in 21 per cent. of those without, a difference that just reaches the 5 per cent. level of significance.

The frequency of uveitis is thus about six times that found in rheumatoid arthritis (Sorsby and Gormaz, 1946), so that a history of iritis or the presence of posterior synechiae is of considerable diagnostic importance in any obscure case of backache.

(2) *Chest Complications*.—The clinical diagnoses of those patients with pulmonary complications are listed in Table XV. These do not differ a great deal from the pulmonary complications seen in a series of patients with rheumatoid arthritis by Aronoff, Bywaters, and Fearnley (1955).

TABLE XV  
CLINICAL DIAGNOSES PERTAINING TO THE LUNGS IN 212 PATIENTS WITH ANKYLOSING SPONDYLITIS COMPARED WITH THE 253 CASES OF RHEUMATOID ARTHRITIS ALSO FROM HAMMERSMITH HOSPITAL (Aronoff and others 1955)

Clinical Diagnosis of Lung Disease	Series	
	Ankylosing Spondylitis	Rheumatoid Arthritis
No apparent disease .. ..	190	180
Bronchitis alone .. ..	9	26
Bronchitis and asthma .. ..	4	3
Bronchitis and emphysema .. ..	2	12
Emphysema alone .. ..	0	8
Bronchiectasis .. ..	3	6
Pulmonary tuberculosis .. ..	10	7
Pulmonary fibrosis .. ..	0	5
Bronchial carcinoma .. ..	2	2
Spontaneous pneumothorax .. ..	1	0
Cyst of mediastinum .. ..	1	0
Other conditions .. ..	0	15
Total Cases .. ..	212	253

105 of the present patients had one or more chest x-ray examinations, and here again the results are similar to the findings of Aronoff and others (1955) in 130 patients with rheumatoid arthritis and a



control group of non-rheumatoid patients (Table XVI).

TABLE XVI

RADIOLOGICAL LUNG CHANGES IN PRESENT SERIES OF 212 SPONDYLITICS COMPARED WITH FINDINGS OF ARONOFF AND OTHERS (1955) IN PATIENTS WITH RHEUMATOID ARTHRITIS AND NON-RHEUMATOID CONTROLS

Radiological Lung Changes	Series		
	Ankylosing Spondylitis	Rheumatoid Arthritis	Controls
No lesion ..	83	68	76
Bronchitis and pneumonia ..	5	20	18
Emphysema ..	2	13	4
Bronchiectasis ..	2	4	2
Pulmonary tuberculosis ..	10	14	22
Pulmonary fibrosis ..	1	6	0
Bronchial carcinoma ..	2	2	8
Cyst of mediastinum ..	1	0	0
Other conditions ..	0	21	12
Cases X-Rayed ..	105	130	130
Cases not X-Rayed ..	117	123	0
Total Cases ..	212	253	130

This study does not confirm the suggestion that patients with ankylosing spondylitis, because of their limited respiratory excursion, are usually more susceptible to respiratory infections (Hamilton, 1949). However, the spondylitic may run a slight risk because quiescent pulmonary tuberculosis may be exacerbated by radiotherapy. This sequence was seen in two of the present patients with ultimately fatal results. In both cases *x* rays before treatment showed no active disease but extensive pulmonary tuberculosis was found at 5 and 15 months after treatment.

(3) *Haematological Complications.*—Although most patients had a blood count when attending for their follow-up visit, only twelve showed haematological disorders. Eight had a hypochromic or normochromic anaemia, and three megaloblastic anaemia. Mild anaemia is considered to be frequent in ankylosing spondylitis, but was not observed here, possibly because most of the patients were observed at a late stage. One patient died from Hodgkin's disease. Another patient (Case 5) developed leukaemia six years after his first course of radiotherapy. As Court Brown and Abbatt (1955) have shown, there is an increased risk of leukaemia following spinal radiation for ankylosing spondylitis, particularly after multiple courses of radiotherapy.

Case 5, a male chauffeur aged 43 years in 1955, began to experience sacro-iliac pain in 1940, shortly after entering military service. This was treated symptomatically for 2 years until an attack of dyspepsia precipitated his

admission to hospital and a "bamboo spine" was noticed during the course of a barium meal. Following discharge from the forces he continued to have backache and stiffness until 1949 when he was treated by radiotherapy (1,000r to each of four spinal fields). This gave partial relief, but a further course (1,000r to each of five spinal fields) was more effective. The patient did light work without discomfort until 1955 when he was admitted to hospital for investigation of anaemia. This was found to be due to myeloblastic leukaemia and he died shortly afterwards.

(4) *Gastro-intestinal Complications.*—Since most of the drugs used in the treatment of ankylosing spondylitis may cause dyspepsia, its occurrence in 24 patients during the course of their spondylitis is not surprising. This association has been emphasized by Morrison (1955). In three patients their dyspepsia was due to neoplasm (stomach and pancreas), in thirteen to peptic ulcers demonstrated on *x* ray or *post mortem*, and in one to oesophagitis. Four patients had negative barium meal examinations and three were not *x* rayed. Three of these patients first noticed dyspepsia while taking phenylbutazone, and when the drug was withdrawn the dyspepsia subsided.

According to Doll and Jones (1951), the incidence of peptic ulcer in the adult male population of London is between 5 and 10 per cent. The figure of thirteen male patients in the present series is not greater than this normal incidence. Four patients suffered from ulcerative colitis and one from Crohn's disease. This compares with an incidence of three cases of ulcerative colitis in a series of 117 spondylitics reported by Romanus (1953). Though the frequency of ulcerative colitis in the general population is uncertain, Kantor (1929) found only nine cases in 1,000 patients with gastro-enterological complaints, and Spriggs (1934) mentions five cases in 1,000 hospital admissions. It seems therefore that there may be an association between ulcerative colitis and ankylosing spondylitis.

(5) *Spinal Fractures and Subluxations.*—These rarely complicate ankylosing spondylitis; however, Sharp and Purser (1957) have recently drawn attention to an easily overlooked complication, *viz.* spontaneous atlanto-axial subluxation. They suggest that this should be considered in any spondylitic with pain or deformity in the cervical region, whether or not neurological signs are present.

In the present cases there were no patients with cervical spine fractures, but one patient complaining of neck pain was found to have atlanto-axial subluxation (Fig. 12, opposite).

Two further patients had fractures of the lumbar spine, one following an injury and the other (Case 6) spontaneously in a porotic spine (Fig. 13, opposite).

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Case 6, a housewife aged 37 years in 1952, was treated in hospital for 7 months at the age of 13 for an attack of polyarthritis diagnosed as rheumatic fever. Only 4 months after her recovery she began to suffer from sacro-iliac pain and at the age of 17 radiological changes were demonstrated in the sacro-iliac joints. During the next 20 years she received three courses of deep x-ray therapy with considerable relief of pain but without preventing ankylosis of the spine. At the age of 30 she became pregnant and the disease remitted, but 4 months after a normal delivery she suffered an exacerbation with transient peripheral arthritis. After the age of 36 she developed progressive kyphosis with angulation at the upper lumbar region, and the x rays showed extremely porotic vertebral bodies with a crush fracture of the second lumbar vertebra. This was confirmed after death one year later which was due to an exacerbation of bronchiectasis or cor pulmonale. Neither clinically nor at *post mortem* was there any evidence of rheumatic heart disease. The sister of this patient is also included in this series.

(6) *Psoriasis*.—Four patients suffered from extensive psoriasis of the body and limbs, beginning before or at the same time as the spondylitis. Three of them showed peripheral joint lesions, especially of



Fig. 13.—Crush fracture of a porotic lumbar vertebra in a patient with long-standing ankylosing spondylitis.



Fig. 12.—Atlanto-axial subluxation in a patient with ankylosing spondylitis.

the hands and feet, progressing in two cases to arthritis mutilans and ankylosis of the metatarsophalangeal and interphalangeal joints. The terminal interphalangeal joints were involved in two patients. The spondylitis was otherwise quite typical and three patients treated with radiotherapy responded well.

Two of the above patients suffered from ulcerative colitis and psoriasis as well as ankylosing spondylitis with peripheral joint involvement.

(7) *Urethritis*.—Eight patients gave a history of urethritis before and one shortly after the onset of the spondylitis. No case presented the full picture of Reiter's disease, but in four of these patients the urethritis and peripheral arthritis coincided. Five patients suffered from uveitis. There were no clinical, serological, or radiological features which would differentiate these cases from the remainder of the series, but of the eight patients treated with radiotherapy only four benefited.

(8) *Cardiovascular Complications*.—Cardiovascular lesions were found in sixteen patients (Table XVII). Only three showed chronic rheumatic valvular lesions, though a history of past "rheumatic fever" was fairly common (25 patients). However, eleven of these patients described a chronic arthritis, often with permanent sequelae and followed by intermittent backache. It seems that any arthritis in a young person is likely to be called rheumatic fever and this applies particularly to ankylosing spondylitis with a peripheral joint onset.

TABLE XVII  
CARDIOVASCULAR COMPLICATIONS IN 222 PATIENTS  
WITH ANKYLOSING SPONDYLITIS  
(DETECTED CLINICALLY)

Ischaemic heart disease .. .. .	4
Pericarditis .. .. .	2*
Rheumatic valvular disease .. .. .	2
"Rheumatoid aortitis" .. .. .	2
Hypertensive heart failure .. .. .	1
Cor pulmonale .. .. .	1
Intermittent claudication .. .. .	1
Total .. .. .	13

\* Further lesions, discovered only at *post-mortem* examination included adherent pericardium (two patients) and a sclerosed mitral valve (one patient).

Two patients developed lone aortic incompetence while under observation at intervals of 7 and 12 years after the onset of their spondylitis, and these are to be separately reported. In both cases there was peripheral joint involvement and cardiograms showed prolongation of the PR interval, to 0.25 and 0.24 sec. respectively. Neither showed subcutaneous nodules. Wassermann and *Treponema pallidum* immobilization tests were negative. It

seems probable that these two patients suffer from what Bauer, Clark, and Kulka (1951) have called "rheumatoid aortitis".

Two patients developed transient pericarditis during the course of their spondylitis and two further patients showed extensive pericardial adhesions *post mortem*.

(9) *Pregnancy*.—This does not seem to have the same uniformly favourable influence on ankylosing spondylitis as on rheumatoid arthritis, for only three out of seven patients noted improvement during pregnancy. In four the spondylitic symptoms persisted or were aggravated during the course of eight pregnancies. One further patient dated the onset of her spondylitis from the post-puerperal period.

### Discussion

It may be questioned whether comparisons between different disease duration groups can be used to deduce the course of a disease. For example, patients first attending hospital when symptoms have been present for more than 5 years (rather more than half of the present cases) may represent only those in whom the disease has progressed and may not include those who have become quiescent during this period. This would give an unfavourable bias to interpretations of the course of the disease. Furthermore, with such comparisons it is difficult to assess the effect of increasing age, which quite apart from the disease is likely to affect a patient's functional capacity and employment. Therefore, the present findings were carefully analysed in an attempt to evaluate these two complications.

Table II shows that the type of case referred to hospital during the period 1940-1955 did not vary except in the one respect that the patients seen during 1951-1955 showed a significantly better initial functional status ( $p < 0.05$ ) than did the earlier cases. If the course of ankylosing spondylitis is truly progressive, it would be expected that those patients followed for longer periods will have deteriorated more than patients recently seen, and this seems to be so.

Table XVIII (opposite) shows the mean functional status, the mean employment index, and the mean deformity index (graded as in Figs 8, 9, and 10) derived from the recent follow-up data, correlated with the time of first attendance. Each index falls (*i.e.* deterioration occurs) with increasing length of follow-up, and calculations based on the actual numbers of patients show the differences to be significant ( $p < 0.05$ ) in each instance. A similar change is seen in chest expansion.

Furthermore, each follow-up group has been



TABLE XVIII

MEAN STATUS WITH REGARD TO FUNCTIONAL ABILITY, EMPLOYMENT, AND DEFORMITY AT FOLLOW-UP, IN 211\* SPONDYLITIC PATIENTS GROUPED ACCORDING TO TIME WHEN FIRST SEEN AND DURATION OF SYMPTOMS WHEN FIRST SEEN. GRADES OF FUNCTION, EMPLOYMENT, AND DEFORMITY ARE THOSE DEFINED IN FIGURES 8, 9, AND 10. PATIENTS NOW DEAD WERE GRADED ACCORDING TO THEIR STATE BEFORE THE TERMINAL ILLNESS

Time when First Seen	1940-45				1946-50				1950-55			
Duration of Disease when First Seen (yrs) . . . . .	0-5	6-10	Over 10	Mean	0-5	6-10	Over 10	Mean	0-5	6-10	Over 10	Mean
"Mean" Functional Status (Range from 5 Good to 1 Bad) . . . . .	3.4	3.1	1.8	3.0	3.4	3.6	3.1	3.4	3.8	3.8	3.6	3.7
"Mean" Employment Index (Range from 4 Unchanged to 1 Unemployed) . . . . .	2.2	1.6	2.0	2.0	2.5	2.8	2.8	2.7	3.4	3.0	2.7	3.0
"Mean" Deformity Index (Range from 4 No Deformity to 1 Severe) . . . . .	2.5	2.4	1.3	2.3	3.1	3.0	1.9	2.7	3.3	3.2	2.7	3.1

\* One further patient was omitted because duration of illness was not known.

subdivided according to the duration of symptoms when first seen. Here again there is a constant deterioration when, for instance, the patients with symptoms of short duration and first seen during 1951-1955 are compared with the corresponding group first seen during 1940-1945. Such a comparison suggests that the deterioration is genuine and not due to selection bias. If the Table is compiled for those living at the time of follow-up only, similar trends are seen.

However, this deterioration might simply be due to advancing age, since the average age of the 1- to 5-year duration group shown in Figs 8, 9, and 10 was 32.3 years compared with 51.6 years for the group which had had symptoms for more than 20 years.

In order to reduce this age factor, those patients aged 31-50 years in January, 1956, were analysed separately. Here again there was a slight deterioration in functional status and employment status with increasing duration of symptoms but the differences were not statistically significant. The figures for deformity, however, showed a more striking and statistically significant increase ( $p < 0.01$ ) with increasing duration of symptoms.

If the foregoing data is now used to indicate the course of ankylosing spondylitis the following picture emerges.

In most instances the onset is insidious with initial symptoms in the lower spine or peripheral joints, the latter being more common in adolescents. At this stage there has always been evidence of sacro-iliac involvement in our cases, though a few are recorded in the literature with such changes only subsequently.

The disease then progresses by a series of exacerbations and remissions. Although it is usually considered that the disease may become completely arrested at any stage, the present study suggests that this is exceptional. In many cases the spine gradually becomes more extensively involved, deformity more marked, and chest expansion more limited, over periods up to 30 years. In many patients with apparently quiescent disease, attacks of iritis continue. Almost one-half of the total group show a raised erythrocyte sedimentation rate at follow-up, which further suggests that the disease is not really inactive.

On the other hand, root and peripheral joint involvement tends to occur in the early years of the disease and, although established peripheral joint lesions usually progress, it is uncommon for new peripheral joint lesions to appear after the first 10 years of the illness. This strange divergence of behaviour in the spinal and peripheral joints is difficult to explain. While the basic inflammatory mechanism is probably the same for both sets of joints, it may be that the progress and type of lesion is influenced by the stresses and strains sustained. Thus the weight-bearing joints tend to be affected far more frequently than the non-weight-bearing joints. This would explain the progression of the disease in the spine, which continues to transmit weight even after the spondylitic becomes chairbound. On the other hand, as the disease advances and the patient's activities become more restricted, less burden is imposed upon the extra-spinal joints.

Throughout the course of the disease there is a very slow decline in the patient's functional capacity, but in the absence of a control group of normal



subjects it is difficult to be certain whether this is due to the disease or to advancing age. After a few years, patients can no longer indulge in heavy physical labour or recreation and after 10 years of illness, most spondylitics are reduced to sedentary or light occupations. Nevertheless, most patients continue to be fully employed and self-supporting for decades after the onset of symptoms and the disease only rarely seems to shorten life.

The main factor influencing the prognosis is the presence or absence of extraspinal joint involvement, for this is considerably more disabling than spinal arthritis, especially when it affects the weight-bearing joints. If the disease begins after the age of 30 years, or if symptoms have been present for 10 years without evidence of extraspinal joint involvement, the patient will probably escape with a rigid spine but without extraspinal joint lesions. If radiotherapy is to be used, then in our experience it will give better symptomatic results if used early, before there is evidence of extensive spinal involvement. In view of the potential risk of leukaemia (Court Brown and Abbatt, 1955), only those spinal areas which are causing symptoms should be treated, thus exposing a minimum of haemopoietic tissue to the irradiation. Multiple courses of radiotherapy should be eschewed.

We have viewed this group as a single entity, since we have not found consistent differences between such subgroups as Sharp (1957) has differentiated, on the basis of association with rheumatic fever or its consequences, psoriasis, rheumatoid arthritis, or urethritis (Reiter's disease), but our case material is less than half that collected by Sharp:

(1) **Rheumatic Heart Disease.**—If we separate off the two cases with late developing aortic valvulitis, as described by Bauer and others (1951), the incidence of rheumatic valvulitis (*i.e.* with mitral involvement), is so low in our series (1.4 per cent.) that it can safely be ascribed to coincidence. Although 25 patients gave a history of a previous illness diagnosed as rheumatic fever, eleven of them described it as a chronic peripheral arthritis, often with permanent sequelae and followed by intermittent backache. It was probably the beginnings of ankylosing spondylitis. The peripheral arthritis in such cases did not resemble that described by Bywaters (1950) as "Jaccoud's syndrome". Further, while there is no inherent unlikelihood in a Jaccoud-type fibrosis affecting the spine as well as the peripheral joints, as postulated by Thomas (1955), we have not been able to recognize in our cases the radiological peculiarities of the central joints described by Thomas (1955) and by Sharp (from the same material, 1957), *i.e.* "small erosions of the sacro-iliac joints with spotty areas of sclerosis, irregularity and fusion of the apophyseal joints, narrowed intervertebral disk spaces with increased height of the vertebral bodies". Nor have we seen the normal chest

expansion and tendon nodules described by Sharp (1957) in such cases. Indeed, Case 7, one of our otherwise typical cases of ankylosing spondylitis, without peripheral joint lesions or heart lesions and without evidence of previous rheumatic fever, has a peculiar cervical spine (Fig. 14) very closely resembling one claimed to represent a Jaccoud's syndrome of the spine (Thomas, 1955; Case 27, Fig. 3). It seems possible that such tall, narrow vertebrae may be due to interference with growth at the ring epiphyses before they unite and may thus date the lesion (see similar growth defects in Still's disease; Ansell and Bywaters, 1956).

**Case 7, a male ex-shop assistant aged 49 years in 1956,** had noticed aching pains in the buttocks and thighs when aged 19 years, which later spread to the remainder of the spine. At the age of 33 years the whole spine was rigid and movement at the hip joints was limited. He received various treatments, including radiotherapy to the whole spine and both hip joints, with considerable relief of pain. There was no history of rheumatic fever or of peripheral joint involvement and the heart was clinically normal. When last seen in 1956 a sedimentation rate was 3 mm./hr (Westergren), and a sheep cell agglutination test was negative. An x ray of this man's cervical spine is shown in Fig. 14.



Fig. 14.—Cervical spine of a patient with ankylosing spondylitis beginning at the age of 19 years. Note abnormal shape of vertebral bodies, possibly due to abnormal growth at ring epiphyses.

(2) "Psoriatic Spondylitis".—The association of psoriasis with ankylosing spondylitis, emphasized recently by Fletcher and Rose (1955), again did not appear to produce any easily recognizable subgroup. The incidence of psoriasis in our series was 1·8 per cent. (4 in 222) compared with 4 in 100 (Fletcher and Rose). While ankylosis of the small finger and toe joints occurred in two of these, we have also seen this occur in long-standing ankylosing spondylitis not associated with psoriasis. The terminal interphalangeal joints were affected in two of the patients with psoriasis but in none of the other patients.

(3) "Rheumatoid Spondylitis".—In Great Britain, ankylosing spondylitis is thought to be a separate entity from rheumatoid arthritis, distinguished by age and sex incidence, negative Rose test, frequent presence of uveitis, absence of nodules, and good response to radiotherapy. While it is recognized that the cervical spine is frequently involved in rheumatoid arthritis, involvement of the lower spine and sacro-iliac joints is seldom seen.

Spondylitis with sacro-iliac joint involvement due to rheumatoid arthritis as distinct from ankylosing spondylitis, was not recognized in this series, although, in one patient, pericarditis and multiple subcutaneous nodules of the rheumatoid type (but with a negative Rose test) coming on with peripheral joint involvement some 24 years after a typical ankylosing spondylitis, inclined us to postulate the presence of both diseases. While the morphology of peripheral joints in this case resembled that of rheumatoid arthritis, the same is true of otherwise typical ankylosing spondylitis with peripheral joint involvement. We were unable to distinguish a rheumatoid sacro-iliitis radiologically, as described by Sharp (1957).

(4) "Reiter's Spondylitis".—The acquisition of a gleet as a sign of attaining manhood is no longer as popular and as widespread as it was in Boswell's time but, in a predominantly young male group, more than urethritis (or a history of it) and ankylosing spondylitis should be deemed necessary to make a "Reiter's spondylitis" (Sharp, 1957). While nine of our cases admitted to past urethritis when directly questioned, in only three did the arthritis develop soon after an attack of urethritis. Though five of these patients also developed uveitis, this occurred several years after the urethritis. No patient showed keratoderma and the spondylitis was in no way unusual. In only two patients were the feet and ankles affected.

The occurrence of ankylosing spondylitis following Reiter's disease is now well known, and Ford (1953) found four such cases among patients with "venereal arthritis" attending the London Hospital.

It is of interest that Romanus (1951) has tried to incriminate chronic urogenital infection in the aetiology of ankylosing spondylitis; this occurred in a majority of his series of 117 male Swedes, and Romanus has suggested that infection or toxic products reach the spine by way of the prevertebral veins but that arthritis only results if other factors are present, notably a familial diathesis.

Such a hypothesis does not explain the peripheral joint lesions.

The essential lesion in ankylosing spondylitis appears to be involvement of the apophyseal joints: it seems likely that bambooing is secondary and could result from immobilization of the spine together with local inflammatory disease due to any cause. Thus, bridging is seen locally with almost any focal inflammatory spinal lesion. While, therefore, it appears possible for ankylosing spondylitis to occur following colitic, psoriatic, "Reiter's", rheumatoid, or "Jaccoud's" disease of the apophyseal joints, just as it may follow local brucellar involvement, we have not felt in this comparatively limited survey that we could distinguish any such subtypes, either on radiological or on clinical grounds. The general pattern of disease as shown in this series is remarkably uniform.

### Summary

212 out of 222 patients suffering from ankylosing spondylitis and treated at the Hammersmith Hospital between January, 1940, and December, 1955, have been traced and studied. Their present physical and functional state suggests that ankylosing spondylitis is usually a slowly progressive condition without permanent complete remission. Spinal involvement, deformity, and limitation of chest expansion all show slow but progressive deterioration with increasing duration of the disease. Iritis continues to recur and a raised erythrocyte sedimentation rate is frequent even in long-standing and apparently inactive cases. However, in the later stages of the illness, the tempo of the disease process is retarded, and it is unusual to find new peripheral joint lesions or first evidence of iritis at this stage.

Despite illness of more than 20 years' duration, a patient's functional capacity may be remarkably little impaired when one makes allowance for age; 63 per cent. of the living patients were employed in full-time light occupations, whereas only 18 per cent. were severely deformed.

200 of these patients had received radiotherapy on one or more occasions; it did not seem to arrest disease activity more than temporarily. The proportion of patients with a symptomatic relapse after radiotherapy rose from 67·4 per cent. at one year after treatment to 90 per cent. after follow-up periods of more than 10 years.

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### Caractères cliniques et évolution de la spondylarthrite ankylosante, d'après l'observation de 222 cas vus à l'hôpital

#### RÉSUMÉ

On a retrouvé et re-examiné 212 sur 222 malades atteints de spondylarthrite ankylosante et traités à l'hôpital Hammersmith (Londres) entre le mois de janvier, 1940 et le mois de décembre, 1955. Leur état physique et fonctionnel présent suggère que la spondylarthrite ankylosante est habituellement une maladie lentement évolutive, sans remission complète et permanente. L'implication de la colonne vertébrale, la déformation et la limitation de l'expansion de la poitrine accusent une détérioration lente mais constante avec le temps. L'irite revient toujours et la vitesse de sédimentation globulaire élevée est fréquente même dans les cas anciens et apparemment inactifs. Cependant, à des périodes plus avancées de la maladie, le tempo du processus morbide est ralenti et il est alors très rare de trouver une lésion dans une articulation périphérique nouvelle ou le commencement d'une irite.

Même lorsque la maladie dure 20 ans ou plus, la capacité fonctionnelle du malade peut se trouver remarquablement peu altérée, pourvu qu'on tienne compte de son âge; 63% des malades survivants avaient un emploi léger mais à pleines journées et 18% seulement avaient des difformités sévères.

Deux cents de ces malades ont reçu de la radiothérapie une fois ou plus; cela ne semblait arrêter l'activité morbide que temporairement. La proportion des malades ayant une rechute symptomatique après la radiothérapie monta de 67,4% au bout d'un an à 90% au bout de 10 ans.

### Rasgos clínicos y evolución de la espondilartritis anquilosante, según la observación de 222 casos vistos en hospital

#### SUMARIO

Se revistaron 212 de los 222 enfermos con espondilartitis anquilosante, tratados en el hospital de Hammersmith (Londres) entre enero de 1940 y diciembre de 1955. Su estado físico y funcional presente sugiere que la espondilartitis anquilosante es generalmente una enfermedad lentamente evolutiva, sin remisión completa y permanente. La implicación de la columna vertebral, la deformación y la limitación de la expansión del pecho acusan un deterioro lento pero constante con el tiempo. La iritis vuelve a recurrir y la velocidad de sedimentación eritrocitaria es frecuentemente alta hasta en los casos y aparentemente poco activos. Sin embargo, en los períodos más adelantados de la enfermedad, el proceso mórbido se ve retardado y entonces lesiones de una articulación periférica nueva o el comienzo de una iritis son raras.

La enfermedad puede durar 20 años o más, con notablemente poca alteración de la capacidad funcional, provisto que se tome en cuenta la edad del enfermo; el 63% de los enfermos sobrevivientes tenían una ocupación leve pero constante y tan sólo un 18% tenían deformaciones severas.

Dos cientos de estos enfermos recibieron radioterapia una vez o más; esto no pareció detener la actividad mórbida más que temporariamente. La proporción de los enfermos sufriendo una recaída sintomática después de la radioterapia subió de un 67,4% al cabo de un año a un 90% al cabo de 10 años.



# MEASUREMENT AND INTERPRETATION OF SYNOVIAL FLUID VISCOSITIES

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The highly viscous nature of synovial fluid is one of its most striking physical properties. Since the viscosity is altered in many joint diseases (Ropes and Bauer, 1953) and pathological fluid is usually obtainable without difficulty, one would expect that the determination of viscosities would be a common procedure. In fact, this is rarely undertaken, either because many of the measuring techniques advocated in the literature seem very elaborate or because the figures obtained are difficult to interpret. By using simple apparatus and recording the findings graphically, however, results may be achieved that are of value in assessing objectively the progress of articular disease or the response to therapy.

### Material

Synovial fluid was aspirated from the apparently normal knee joints of six *post-mortem* subjects, within 3 hours of death. All were under 40 years of age, showed no oedema, and died of non-articular conditions. Although such fluid could not strictly be regarded as "normal", it was considered that aspiration of healthy joints during life was unjustifiable. Fluid was also obtained, under general anaesthesia, from the joints of two sacred baboons, the only large primate species available. In addition, fluid was aspirated from the diseased knee joints of patients who were receiving intra-articular medication.

### Methods

All fluids were brought to a temperature of 20° C. and the viscosities estimated the same day. A modification of the apparatus and technique described by Davies (1944) was used (Fig. 1).

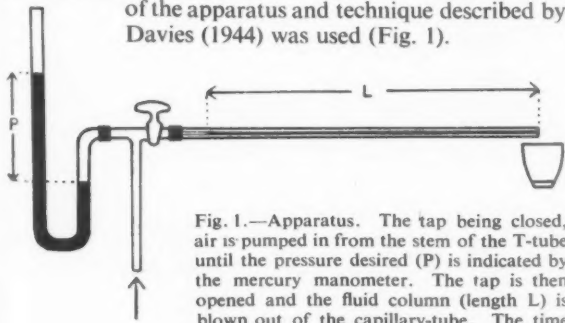


Fig. 1.—Apparatus. The tap being closed, air is pumped in from the stem of the T-tube until the pressure desired (P) is indicated by the mercury manometer. The tap is then opened and the fluid column (length L) is blown out of the capillary-tube. The time (T) for complete expulsion of the fluid depends on its viscosity.

A capillary-tube of known, uniform radius (R cm.) was filled almost completely with the fluid under test and placed in a horizontal stand. The length of the column of fluid was measured (L cm.), and one end of the tube was connected to a manometer and pump by means of a T-piece fitted with a tap. This was kept closed until the manometer indicated that the pump had raised the pressure to a predetermined level (P cm. Hg). It was then opened and the pump was started again momentarily to restore the pressure level. The fluid was expelled from the tube into a small container, the time (T sec.) for complete expulsion being measured with a stop-watch. The experiment was repeated at least eight times using different pressures, so that the times ranged evenly from a few seconds up to 2 or 3 minutes. The fluid that accumulated in the container could be used again if the total quantity available was very small.

The following formula was used to calculate the viscosities:

$$\text{Viscosity in poises} = \frac{3,307 \times P \times T \times R^2}{L^2}$$

This equation is over-simplified; for example, it takes no account of surface tension effects (*see* Davies, 1944). However, tests with lubricating oils of known viscosity showed that the error involved did not exceed 10 per cent. of the correct value (Fig. 2). The correct equation includes certain constants, for example, the specific gravity of mercury; these are incorporated in the amount

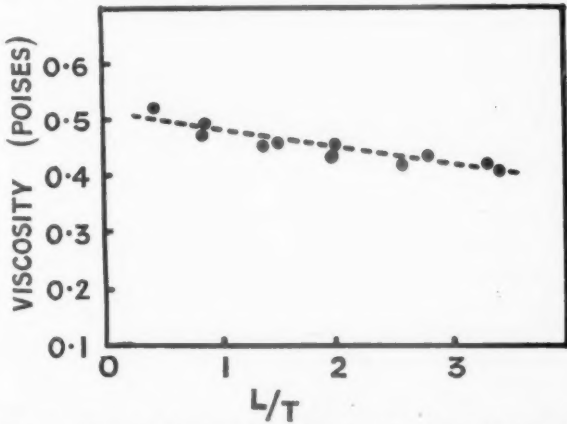


Fig. 2.—Viscosity of a standard lubricating oil as determined by the present technique. There is apparently a very slight fall in viscosity when the fluid is expelled more quickly, *i.e.* as the rate of shear between adjacent molecules of the fluid increases (*see* text).

\* In receipt of a grant from the Nuffield Foundation.



3,307 above. If one capillary-tube is always used,  $R$  is also constant; 0.0325 cm. is a suitable standard radius.

The viscosity of some fluids was measured by means of a rolling-ball viscometer (Barnett, 1957). This gave the value at high rates of shear.

### Results

Like other disperse systems, synovial fluid exhibits non-Newtonian properties unless it is very dilute (Hermans, 1953; Ogston and Stanier, 1953). It behaves as an extremely thick oil when joint surfaces are being sheared very slowly upon one another, but becomes progressively less viscous as the rate of shear increases. Thus, in the capillary-tube method used here, a low figure for the viscosity is obtained if a high expulsion pressure—which empties the tube rapidly—is applied. On the other hand, if the pressure is low, the fluid may take many minutes to be expelled—longer than the thickest lubricating oil in general use.

This anomalous viscosity may be expressed in several ways (Ogston and Stanier, 1953; Sunblad, 1954; Blair, Williams, Fletcher and Markham, 1954). A simple method used by the author was to plot the various viscosity readings against the corresponding average rate of expulsion of the column of fluid (*i.e.*  $L/T$ ). Admittedly, this method introduced an undesirable feature in that both the factors  $L$  and  $T$  were invoked twice—once in the formula for calculating the viscosity, once in the term for the rate of expulsion. However, this defect was outweighed by the ease of interpretation of the results, for it can readily be understood that the fraction  $L/T$  is an index of the "rate of shear" of the molecules of fluid upon one another and upon the inner surface of the capillary-tube.

The curves obtained were very similar to those published by Ogston and Stanier (1953), in which the calculated viscosities were plotted against the rate of shear of synovial fluid between a stationary and a moving curved surface (Fig. 3*a*, 3*b*).

In theory, the points should all lie on a line parallel to the axis of abscissae, if a true (Newtonian) fluid is being tested, for the viscosity should remain constant irrespective of the rate of emptying the tube. The apparent slight fall in viscosity as the rate increased (Fig. 2) resulted from the use of an incomplete formula as well as from defects in the method of graphic representation.

It was found convenient to plot the viscosity figures on double-logarithmic graph paper (Fig. 3*c*); the points then fell along a straight line except at high rates of expulsion. This regression line could be calculated by the method of least squares if desired, but it was usually estimated with sufficient accuracy by eye. The range of scatter in a typical graph is shown in Fig. 3*c*; the points are omitted from other figures. Translucent graph paper was used so that several graphs could readily be compared by superimposition.

Two properties of synovial fluid could be evaluated by studying these graphs. Firstly, the viscosity of a given sample at any particular rate of expulsion was read off and compared with the corresponding figure for a normal fluid or that removed from the same joint at an earlier date. Secondly, the degree of anomalous viscosity was indicated by the slope of the linear graph, which was steep when normal synovial fluid was used but more nearly parallel to the axis of abscissae when the fluid had been taken from arthritic joints. Pathological fluids commonly contain molecules that are incompletely

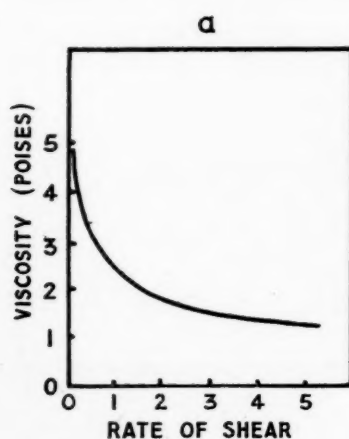


Fig. 3(*a*).—Viscosities of synovial fluid at different rates of shear (after Ogston and Stanier).

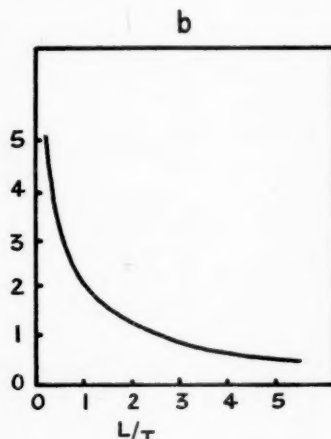


Fig. 3(*b*).—Viscosities of synovial fluid at different average rates of expulsion from the capillary-tube.

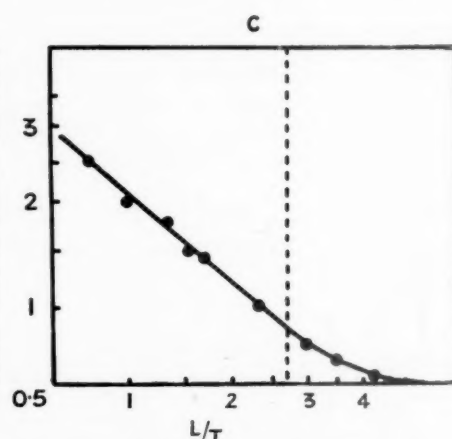


Fig. 3(*c*).—Similar viscosity figures plotted on double-logarithmic scale. All points to the left of the dotted line fall along a straight line.

polymerized (Ragan and Meyer, 1949) and thus behave more like Newtonian fluids.

In Fig. 4 are shown the graphs derived from the knee fluids of the six *post-mortem* subjects and the two living baboons. These normal synovial fluids did not form a homogeneous group, but all were considerably more viscous than the fluids customarily aspirated from arthritic knees.

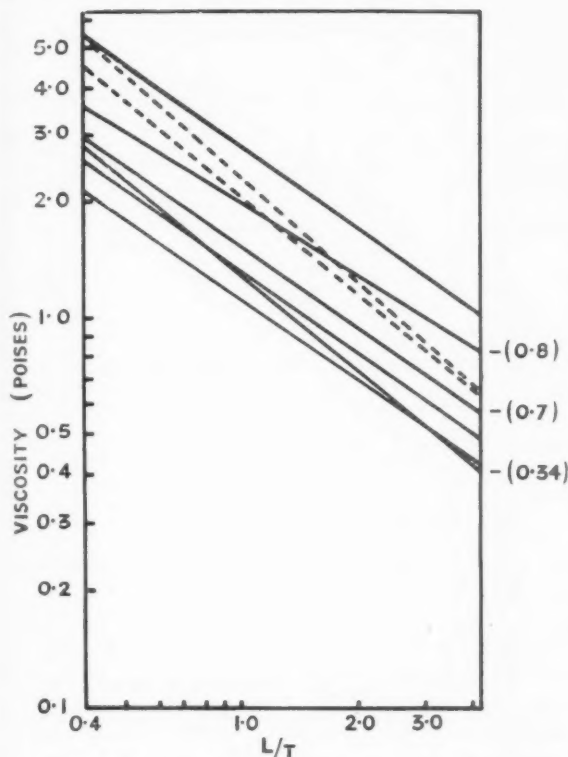


Fig. 4.—Viscosity figures of eight normal synovial fluids determined at different rates of expulsion from the capillary-tube (see text). Note that all fluids behave as if they are much less viscous if the rate of expulsion is increased. Numbers in brackets refer to the viscosities as determined by a rolling-ball viscometer. Baboon fluids dotted.

Serial studies of the knee fluids of two patients are shown in Figs 5 and 6 (overleaf).

Although the synovial fluid viscosity of the latter patient was raised towards the normal figure as a result of the intra-articular therapy, it fell rapidly when treatment was stopped. The former patient showed very little response to treatment, the viscosity remaining subnormal throughout.

There was no evidence that the viscosity of synovial fluid is subject to large irregular fluctuations as is commonly believed. Unpublished observations on a number of other patients indicate that synovial fluid remains sufficiently constant for valid comparison to be made of the viscosities before and after treatment.

Some of the viscosities at high rates of shear, obtained by use of the rolling-ball viscometer, are indicated by numbers in brackets in Fig. 4.

### Discussion

Before considering the interpretation of the results, it is necessary to discuss the statements concerning synovial fluid viscosity that are recorded in the literature. In view of the anomalous properties of the fluid, a single figure (for example, an observation that a particular sample has a viscosity of 0.5 poises) is almost meaningless unless the corresponding rate of shear is also given. For this reason, the findings of Dixon and Bywaters (1953), Bauer, Ropes, and Waine (1940), and many other workers are difficult to evaluate. Single figures may in fact be misleading. Some fluids studied by the author differed considerably at low rates of shear, but—because of unequal degrees of polymerization—had almost identical viscosities at high rates, as determined by the rolling-ball viscometer (see Fig. 4).

Synovial fluid is less anomalous in behaviour at high rates of shear—presumably because the long molecular chains have become untwisted and slide freely upon one another—and some of the recorded figures may refer to the viscosity measured at these high rates. It is doubtful, however, whether such figures have great physiological significance. The maintenance of a viscous synovial film between moving articular surfaces is necessary to prevent excessive wear and tear (MacConaill, 1932; Jones, 1934; Barnett, 1956). A fluid of reduced viscosity may provide adequate lubrication when a joint is moving rapidly but the film is liable to be dispersed as soon as movement is slowed (Charnley, 1954). For this reason the viscosity measured at low rates of shear is more significant than that at high rates.

The degree of polymerization of the hyaluronic acid molecules in synovial fluid is important also. Fully polymerized molecules play an important part in preventing direct contact between articular surfaces that are forcibly compressed together (Ropes, Robertson, Rossmeisl, Peabody, and Bauer, 1947).

One reason why viscosity measurement is not a common procedure in assessing joint disorders is the widespread impression that the fluid within a joint is liable to fluctuate from day to day in its physical properties and to differ markedly from that removed from the corresponding joint of another person. The author believes that this variability has been exaggerated, mainly through a failure to appreciate the properties of non-Newtonian fluids. Thus the scatter in the results obtained by Davies

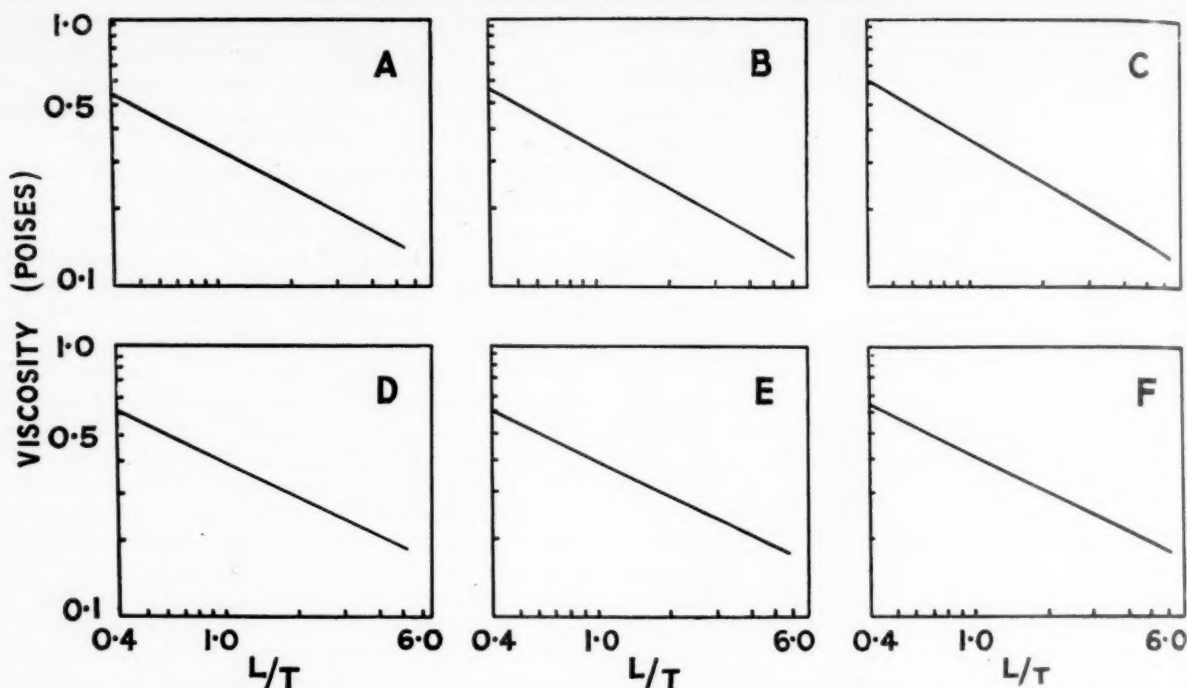


Fig. 5.—Knee fluids of patient A.J. (rheumatoid arthritis).

A. No treatment for 2 months.

B. One week after treatment with drug X.

C. One week later—very slight improvement.

The synovial fluid viscosity is hardly affected by either drug.

D. After 6 weeks without treatment.

E. One week after treatment with drug Y.

F. One week later—very slight improvement.

(1944), based on a large number of measurements in cattle, depends to a considerable extent on the fact that the anomalous viscosity was not taken into account; few workers before Ogston and Stanier (1953) appreciated the importance of this. The remarkable discrepancies in the literature—the normal knee fluid having a viscosity of 0.1 to 0.2 poises according to Kling (1931) and of 5.0 to 15.0 poises according to Schneider (1925)—can also be explained upon this basis. The knee fluids in the present series were much more uniform.

Synovial fluid is only one of the joint tissues—that which is most readily obtained by biopsy. An improvement in the viscous properties of fluids taken at intervals from a pathological joint does not necessarily indicate that all the tissues are recovering. Nevertheless, there is reason to believe that it reflects a lessening of inflammatory processes (Jessar, Ganzell, and Ragan, 1953). Taken in conjunction with other tests, such as those of Fletcher, Jacobs, Rose, Hess, and Markham (1954), and with the clinical picture, viscosity determinations can provide a valuable objective guide to the effect of any new drug that is being tested.

#### Summary

A technique is described for measuring the viscosities of normal and pathological synovial

fluids at different rates of shear. Known pressures are applied to a column of fluid within a capillary-tube, and the rate of expulsion of the fluid is measured. By recording the results graphically on double-logarithmic graph paper, samples of synovial fluid may be compared with respect to viscosity in poises and degree of polymerization of the contained hyaluronic acid molecules.

The literature is discussed with special reference to the importance of obtaining several viscosity readings at low shear rates, when the anomalous properties of synovial fluid are most marked.

I am indebted to Mr. G. Sprigg for supplying many samples of synovial fluid and to Prof. D. V. Davies for helpful advice.

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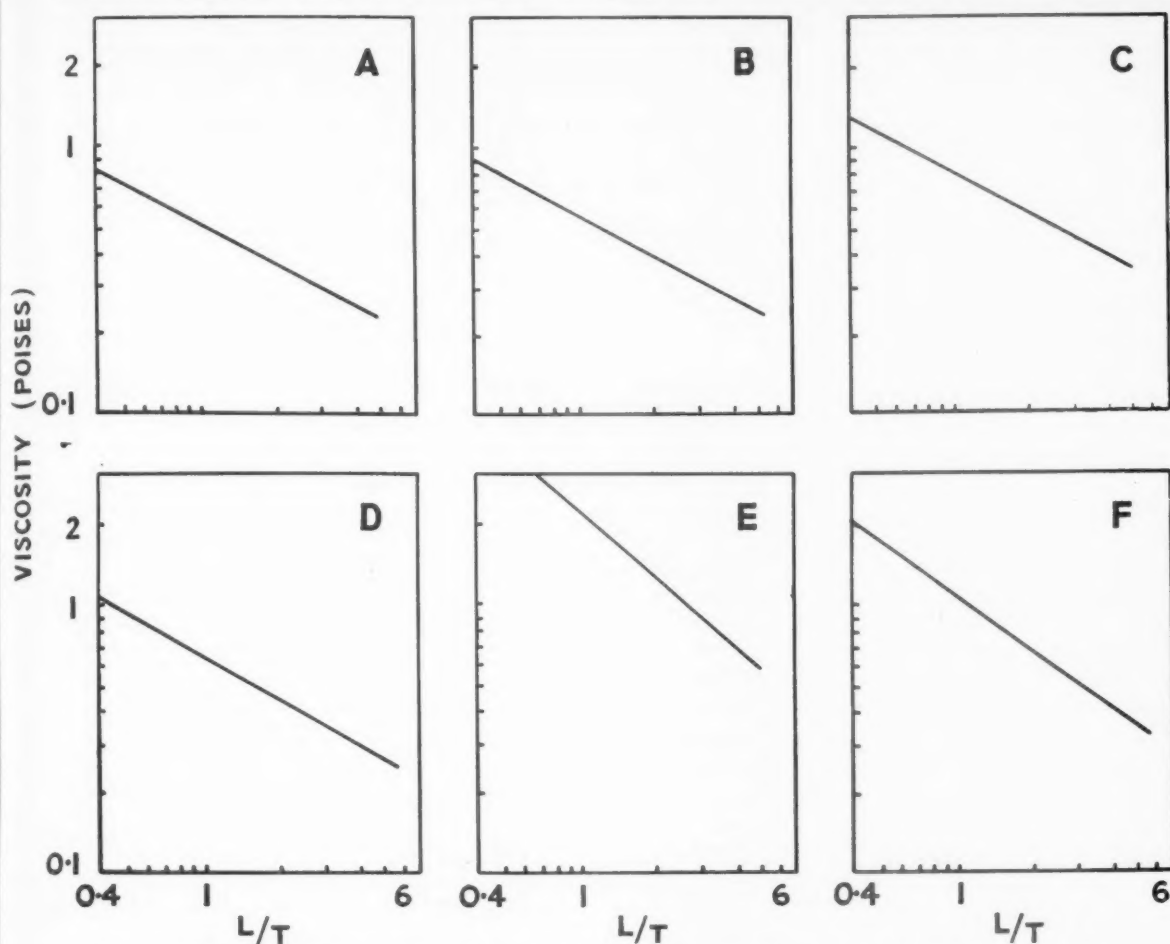


Fig. 6—Knee fluids of patient B.C. (rheumatoid arthritis).

- A. No treatment for 6 weeks.  
 B. One week after treatment with drug X—some improvement.  
 C. One week later—improvement continuing.

Both drugs were effective for a short period, especially Y.

- D. After 6 weeks without treatment—viscosity falling.  
 E. One week after treatment with drug Y—great improvement.  
 F. 2 weeks later—viscosity falling.

Ogston, A. G., and Stanier, J. E. (1953). *J. Physiol. (Lond.)*, **119**, 244.  
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l'importance de plusieurs lectures de viscosité à des taux de cisaillement bas, quand les propriétés anormales du liquide synovial sont le plus prononcées.

#### Medida e interpretación de la viscosidad del líquido sinovial

##### SUMARIO

Se describe un procedimiento para medir la viscosidad del líquido sinovial normal y patológico en valores variables de la fuerza de empuje. Se aplica una presión conocida a una columna de líquido en un tubo capilar y se mide la tasa de su expulsión. Se nota el resultado gráficamente sobre papel logarítmico doble, lo que permite la comparación de los especímenes de líquido sinovial respecto a su viscosidad en poises y el grado de polimerización de las moléculas de ácido hialurónico presente.

Se discute la literatura, particularmente respecto a la importancia de varias lecturas de viscosidad cuando la fuerza de empuje es baja y cuando las propiedades anormales del líquido sinovial son muy marcadas.

#### Mesure et interprétation de la viscosité du liquide synovial

##### RÉSUMÉ

On décrit un procédé pour mesurer la viscosité du liquide synovial normal et pathologique à des taux différents de cisaillement. On applique une pression connue à une colonne de liquide dans un tube capillaire et on mesure le débit d'expulsion du liquide. Après avoir enregistré les résultats graphiquement sur un papier logarithmique double, on peut comparer les échantillons du liquide synovial en ce qui concerne sa viscosité en poises et le degré de polymérisation des molécules d'acide hyaluronique présent.

On discute la littérature, surtout en ce qui concerne



## ESTIMATION OF THE ERYTHROCYTE SEDIMENTATION RATE OF CAPILLARY BLOOD DESCRIPTION OF A NEW METHOD

BY

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Venous blood is necessary for the estimation of the erythrocyte sedimentation rate (E.S.R.) by the methods of Westergren (1921) and Wintrobe and Landsberg (1935), but venepuncture may occasionally prove difficult or impossible, owing to such factors as inadequate veins, obesity, and flexion deformities. A search was therefore undertaken for a reliable method of estimating the E.S.R. using capillary blood. The consensus of opinion (Nichols, 1942) is that under similar conditions the erythrocyte sedimentation rates of capillary and venous blood are comparable.

### Review of Micromethods

Many micromethods are to be found in the literature, and unpublished methods undoubtedly exist. Table I summarizes those methods which seem to be the most widely known; details are also given of two unpublished micromethods and of the Westergren macromethod. Westergren (1957) warns against micromethods, and several other writers believe that the narrow tubes used in certain micromethods cause slowing and irregularity of the sedimenting column of cells (Ham and Curtis, 1938). Thygesen (1942) states that occasionally the E.S.R. is accelerated by narrow tubes. The recommended internal diameter has been variously stated as: over 1.5 mm. (Thygesen), over 2 mm. (Ham and Curtis, 1938), over 2.2 mm. (Westergren, 1957), and 2.5 mm. (Mårtensson and Hansen, 1953). Many authors, however, claim reliable results from methods utilizing tubes of an internal diameter of 1 mm. or even less (Table I). In part these discrepancies may be accounted for by the anticoagulant, as Mårtensson and Hansen and other workers have shown that diluted blood is less likely to be affected by the bore of the tube than blood to which a solid anticoagulant

has been added. Table I (opposite) shows that five micromethods employ tubes of an internal diameter of 2 mm. or over. It is certain that these methods will distinguish normal from abnormal sedimentation rates, but since a micromethod should not need more than 0.3 ml. blood, it is obvious that the wider the bore of the tube the shorter the column must be. It was considered that the results from any micromethod chosen should be capable of accurate conversion at all rates of sedimentation into the corresponding Westergren values, the Westergren method being probably the commonest venous method in use in Great Britain (Dacie, 1956a) and the most reliable (Lawrence, 1953; Duxbury, 1957; and others). In effect, this means that the sedimenting column used in the micromethod must be of the same length as that used in the Westergren method, if Westergren values in the range of 70-130 mm. at 1 hour are to be differentiated; for it is obvious that the maximum possible E.S.R. in mm. at 1 hour will vary directly with the length of the column used. As an example of the undesirability of using a short tube, Nelson and Whyte (1955), using Method 8 (sedimenting column only 38 mm. long), found that "any reading by the micromethod of more than 10 mm. in half an hour or 15 mm. in one hour, may correspond to a Westergren value of anything from 40-140 mm. in one hour". They state that the maximum rate of fall would give a much closer correlation between the methods, but, since multiple readings are inconvenient, it seemed advisable to test the claims of Peters (1945) for the only method (No. 7, Table I) employing a sedimenting column 200 mm. long. Good agreement with the Westergren method is apparent in the values obtained by Peters in thirty patients, though it is not clear from his paper whether he used capillary or venous blood in the smaller tubes.

## ESTIMATING ERYTHROCYTE SEDIMENTATION RATE OF CAPILLARY BLOOD 235

TABLE I  
PARTICULARS OF TWELVE METHODS

Method No.	Authors	Date	Internal Diameter of Tube (mm.)	Length of Sedimenting Column (mm.)	Approx. Volume of Blood Required (ml.)	Anticoagulant	Normal Values	Comment
1	Cutler .. ..	1927	2.5	50	0.3	3 per cent. Na citrate; that amount adhering to walls of tube	A nearly horizontal line	Serial readings must be taken
2	Landau .. ..	1933	1	50	0.04	5 per cent. Na citrate to 12 mm. mark	1-6 mm. ♂ } at 1-8 mm. ♀ } 1 hr	Modification of the Linzenmeier-Raunert method, see also Rogatz (1943)
3	McSweeney ..	1934	1	100	0.08	3.8 per cent. Na citrate; 1 vol. to 4 vols blood	10 mm. at 1 hr (max.)	
4	Smith .. ..	1936	2.5	50	0.3	5 per cent. Na citrate; 1 vol. to 7.5 vols blood	4 mm. at 30 min. (max.) 9 mm. at 1 hr	Modification of Cutler's method
5	Kato .. ..	1938 1940	0.79-1	64-102	0.05	Various dry anticoagulants	0-20 per cent. of length of column at 1 hr	
6	Obermer .. ..	1943	2	100	0.3	Saturated Na oxalate to 4 mm. mark	4 mm. at 15 min. 10 mm. at 30 min. 25 mm. at 1 hr (max.)	Modification of Balachowsky's method
7	Peters .. ..	1945	1.2	200	0.25	3.8 per cent. Na citrate; 1 vol. to 4 vols blood	As for standard Westergren method	Blood taken directly into tube
8	Nelson and Whyte	1955	2.5	38	0.16	3.8 per cent. Na citrate; 1 vol. to 4 vols blood	10 mm. at 1 hr (max.)	Crista apparatus (Messrs. Hawksley, London, W.I). See also Goldberger (1940).
9	Bodian .. ..	Unpublished	2	100	0.3	3.8 per cent. Na citrate; 1 vol. to 4 vols blood	3-10 mm. at 1 hr	Apparatus obtainable from Messrs Hawksley.
10	Masters .. ..	Unpublished	1.5	100	0.2	3.8 per cent. Na citrate; 1 vol. to 4 vols blood	3-10 mm. at 1 hr	Method similar to that used at Hospital for Sick Children, Gt. Ormond Street, London
11	Present Method ..		1.25 ±0.01	200	0.25	5 per cent. Na citrate; 1 vol. to 5 vols blood	2-15 mm. at 1 hr	Modification of Peters' method. Results corrected to correspond to Westergren values
12	Westergren ..	1921 1957	2.5	200	1.6	3.8 per cent. Na citrate; 1 vol. to 4 vols blood	3-5 mm. ♂ } at 4-10 mm. ♀ } 1 hr	

## Results using Peters' Method

Peters used tubes 300 mm. in length; accordingly "Veridia"\* tubes of this length and of 1.25 mm. internal diameter (tolerance  $\pm 0.01$  mm.) were obtained. These tubes have stout walls, and may be put in Westergren stands. A single mark was etched on each capillary tube at 200 mm.

(a) *Venous Blood*.—75 samples of venous blood diluted with 3.8 per cent. sodium citrate in the proportion 4 vols blood to 1 vol. citrate (*i.e.* the Westergren mixture) were put up in Westergren tubes and in Veridia microtubes. Analysis of Table II (overleaf) shows that equivalent readings were obtained, except in the cases marked with an asterisk, throughout the scale of E.S.Rs. The microtubes were no more difficult to read than the macrotubes, and slowing and irregularity of the sedimenting column of cells did not present problems.

\* Obtainable from Messrs. Chance Bros., Ltd., Smethwick Birmingham, 40.

TABLE II  
75 SAMPLES OF VENOUS BLOOD

Tube	Westergren	Micro.
Blood (4 vols.)	Venous (4 vols.)	Venous (4 vols.)
Citrate (1 vol.)	3·8 per cent.	3·8 per cent.
1	2	2
2	3	3
3	4	4
4	4	5
5	5	4
6	5	5
7	5	6
8	6	6
9	6	7
10	7	5
11	7	6
12	7	6
13	7	8
14	7	8
15	8	8
16	8	6
17	8	7
18	8	7
19	8	8
20	8	9
21	8	9
22	8	9
23	9	8
24	9	10
25	10	11
26	10	12
27	10	12
28	11	9
29	11	14
30	12	10
31	12	12
32	12	14
33	12	14
34	13	11
35	13	12
36	13	14
37	15	13
38	16	15
39	18	12*
40	18	14
41	18	17
42	19	14
43	20	12*
44	20	15
45	22	23
46	23	21
47	23	28
48	27	17*
49	27	22
50	28	26
51	29	24
52	29	33
53	30	27
54	30	33
55	32	39
56	36	39
57	37	30
58	37	45
59	40	42
60	41	38
61	41	43
62	48	55
63	48	59
64	48	65*
65	49	56
66	50	47
67	53	70*
68	54	54
69	55	62
70	57	65
71	58	68
72	70	74
73	78	72
74	93	90
75	123	132

Micro=Veridia microtubes, internal diameter 1·25 mm.

\* Results considered unsatisfactory.

(b) *Capillary Blood*.—For these reasons capillary and venous samples from 22 volunteer patients were compared (Table IIIA). In view of the clotting that occurred in two samples of capillary blood (Nos. 19 and 22) 5 per cent. citrate was substituted, the dilution being kept constant, as Ham and Curtis have shown that such a substitution is without effect on the sedimentation rate of venous blood. The results from fifteen further patients are given in Table IIIB.

TABLE III (A AND B)  
CAPILLARY AND VENOUS SEDIMENTATION RATES  
COMPARED IN 37 PATIENTS

Patients Group	A		B	
	Wester- gren	Micro.	Wester- gren	Micro.
Blood	Venous 4 vols.	Capillary 4 vols.	Venous 4 vols.	Capillary 4 vols.
Citrate	3·8 per cent. 1 vol.	3·8 per cent. 1 vol.	3·8 per cent. 1 vol.	5 per cent. 1 vol.
1	2	2	1	5
2	5	9	2	12
3	6	5	3	15
4	7	11	4	25
5	8	6	5	24
6	8	8	6	19
7	9	9	7	31
8	9	11	8	45
9	12	10	9	32
10	12	12	10	40
11	13	18	11	52
12	16	19	12	49
13	20	14	13	51
14	28	36	14	50
15	30	28	15	69
16	30	29		
17	32	32		
18	37	31		
19	41	clotted		
20	48	65		
21	55	79		
22	58	clotted		

The tendency for an accelerated E.S.R. to occur in the microtubes is readily seen, though this effect is not constant. As such a factor would, if constant, aid recognition of slightly increased sedimentation rates, an effort was made to find a citrate concentration and dilution at which this occurred. A number of experiments were performed with venous blood using varying proportions of 3·8 and 5 per cent. sodium citrate. The effect of the addition of the correct quantity of Wintrobe's solid anticoagulant mixture of oxalates (Wintrobe and Landsberg, 1935) was also determined. These experiments led to the following observations:

- (1) A dilution of 5 vols blood with 1 vol. 5 per cent. sodium citrate gave the most reproducible results when compared with the Westergren method. This was therefore adopted as the definite modification of Peters' method.

ESTIMATING ERYTHROCYTE SEDIMENTATION RATE OF CAPILLARY BLOOD 237

(2) Using a solid anticoagulant, the results with these microtubes were invariably slower than the corresponding Westergren values (sometimes by as much as 45 mm./hr).

Description of the Modified Peters' Method

A 0.2 ml. pipette should be calibrated, preferably with mercury, and marks etched at 0.05 ml. and 0.15 ml. (marks "A" and "B"). The pipette is slightly overfilled to mark "A" with 5 per cent. citrate, the end wiped with cotton-wool, and the citrate level adjusted to mark "A". Capillary blood is obtained by ear-lobe puncture with a straight No. 2 Haagedorn needle, after the lobe has been cleaned with spirit and briskly rubbed with dry cotton-wool. Freely-flowing capillary blood is essential, and only the gentlest squeezing is permissible (a second operator to steady the lobe and encourage the flow of blood while the first fills the pipette is a great advantage). The pipette is filled to the 0.2 ml. mark; 0.15 ml. of the blood-citrate mixture is expelled on to a waxed watch glass, and the pipette is then refilled with capillary blood from Mark A to Mark B. In this way, the citrate solution is in contact with the maximum amount of blood. Blood and citrate are then gently but thoroughly mixed and left to stand for 3 to 5 minutes (not longer) in the watch glass, another watch glass of equal diameter being put over it (total volume 0.3 ml.: 0.25 ml. blood, 0.05 ml. 5 per cent. citrate). The microtubes are most conveniently filled to the 200 mm. mark by means of a small teat. An unbroken column free from air bubbles is essential, and this is easily achieved with practice. The tubes are put up in a Westergren stand and read after 1 hour with a millimetre ruler. (When possible, independent readings were made during this trial by two observers; when this was impracticable, the microtubes were read first.) At the completion of the test, the blood-citrate mixture should be run into blotting-paper (as suggested by Montgomery, 1943), as the presence of small clots invalidates the test. The pipette should be cleaned with distilled water, alcohol, and acetone between each sample. The microtubes are conveniently cleaned in the same way and at the same time as the Westergren tubes; that is, with cold tap water and distilled water. Excess water should be shaken out before the tubes are dried in an oven.

(a) Results with Venous Blood.—Venous blood from thirty patients was collected in plain venules\* and diluted immediately with the appropriate

quantity of 5 per cent. citrate solution in the 0.2 ml. pipette as described for capillary blood. The results were compared with those obtained by the Westergren method (Table IVA).

(b) Results with Capillary Blood.—Capillary and venous samples from a further fifty patients were compared (Table IVB). No patient who appeared

TABLE IV (A AND B)  
(A) VENOUS BLOOD DILUTED AS FOR CAPILLARY BLOOD IN THIRTY PATIENTS  
(B) CAPILLARY AND VENOUS SEDIMENTATION RATES (mm.) COMPARED IN FIFTY PATIENTS

Patients Group	A		B	
	Westergren	Micro.	Westergren	Micro.
Tube	Westergren	Micro.	Westergren	Micro.
Blood	Venous 4 vols.	Venous 5 vols.	Venous 4 vols.	Capillary 5 vols.
Citrate	3.8 per cent. 1 vol.	5 per cent. 1 vol.	3.8 per cent. 1 vol.	5 per cent. 1 vol.
1	6	9	1	2
2	8	12	2	3
3	8	16	3	5
4	9	14	4	3
5	14	21	5	4
6	14	24	6	4
7	15	30	7	5
8	17	22	8	5
9	17	41	9	10
10	22	38	10	8
11	29	44	11	13
12	29	53	12	7
13	35	62	13	11
14	39	70	14	13
15	40	53	15	11
16	45	62	16	13
17	45	62	17	14
18	45	65	18	13
19	47	74	19	16
20	51	65	20	18
21	53	77	21	15
22	54	82	22	21
23	55	79	23	24
24	57	92	24	30
25	63	88	25	20
26	70	92	26	21
27	77	95	27	31
28	85	105	28	7*
29	95	125	29	23
30	130	134	30	26
			31	23
			32	15*
			33	32
			34	28
			35	33
			36	37
			37	30
			38	36
			39	41
			40	51
			41	52
			42	53
			43	48
			44	51
			45	54
			46	76
			47	67
			48	90
			49	107
			50	123

\* Obtainable from Bayer Products, Ltd., London.

\* Results unsatisfactory. Blood difficult to obtain: small clots present.



ill was asked to co-operate in this trial, and this accounts for the number of normal values obtained. However, except in the two cases marked with an asterisk, where small clots occurred and results were unreliable, it was observed that:

- (1) The acceleration in the microtubes is constant within narrow limits (Figure) when the Westergren E.S.R. is raised;
- (2) Capillary and venous samples give results that are strictly comparable.

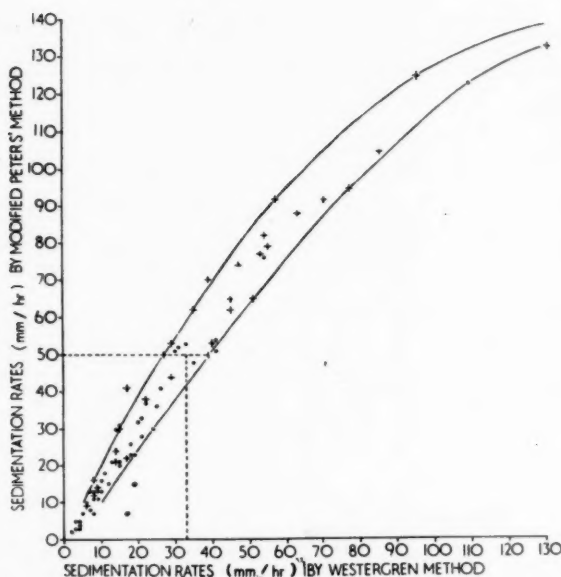


Figure.—Sedimentation rates by Westergren and modified Peters' methods.

From the observed micro-E.S.R., the standard Westergren value may be calculated by taking the mid-point through the curves drawn in the Figure (these limits are curved because of the effect of erythrocyte packing at the higher sedimentation rates). If, for example, the micro-E.S.R. reading is 50 mm./hr, then the Westergren value in over 90 per cent. of cases will be  $33 \pm 6$  mm./hr. It can be seen that though capillary results of 20 and 31 mm. have been found to correspond to Westergren values of 15 mm., these results would have been reported as equivalent to the following Westergren values,  $13 \pm 3$  mm., and  $19 \pm 4$  mm.; indeed, analysis of the most divergent points shows that in no case would the clinician have been significantly misled if the Westergren values as calculated from the micro-E.S.R. values had been the only data available.

In certain cases, serial readings were taken of the cases compared in Table IV at 10-minute intervals. These observations showed that though sedimen-

tation at 10 minutes might be slower in the microtubes, presumably because of a slight prolongation of the phase of aggregation, this relationship was reversed after a further 10 minutes and for the remaining period.

### Discussion

In the 5 months during which this study was in progress, six patients were seen (out of approximately 1,200) in whom venepuncture had been unsuccessfully attempted on at least one occasion in the past. In two, venepuncture was not attempted. In all six patients capillary blood was easily obtainable and their preference for this procedure was emphatic. In these patients, results were obtained that were consistent with the clinical picture, and in no case were differences noted between the behaviour of these micro-E.S.R.s and those which were compared with the Westergren method.

All the patients who volunteered to take part in this study were adults, but this modification of Peters' method could be adapted for paediatric use. Tubes of an internal diameter of 1.25 mm. have given reliable results, and this holds true for samples from non-anaemic patients (Hb 13 to 15 g./100 ml.). This method was designed for estimating the E.S.R. of patients attending a Department of Physical Medicine, and has proved of value in the six cases mentioned.

Puncture of the ear-lobe was used in preference to that of the finger pulp in every patient except one (who had very small lobes). Ear-lobe puncture is less painful and provides blood more readily (Dacie, 1956b). A satisfactory result was obtained from finger-prick blood in the one patient in whom this method was used.

The acceleration that occurred in the microtubes was reproducible when 5 vols blood were diluted with 1 vol. 5 per cent. citrate, and the results obtained were capable of conversion at all sedimentation rates into the corresponding Westergren values with more accuracy than those obtained by the technique described by Peters.

### Summary

An account is given of some common methods employed for determining the erythrocyte sedimentation rate of capillary blood. The claims of Peters (1945) are investigated and a modification of his method is described, that requires 0.25 ml. blood and 0.05 ml. 5 per cent. Na citrate.

From data obtained when results by this method, using capillary blood (fifty patients) and venous blood (thirty patients), were compared with results

by the Westergren method, it is shown that accurate prediction of the Westergren values is possible at all rates of sedimentation with the use of this micro-method.

I should like to thank the patients and physicians of the Arthur Stanley Institute for Rheumatism, Peto Place, London, W.1, for their co-operation; also Dr. M. Bodian of the Hospital for Sick Children, Great Ormond Street, and Dr. P. L. Masters of the Paddington Green Children's Hospital, for descriptions of their methods. I am also most grateful to Mrs. L. Kroll for much technical assistance.

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# Détermination de la vitesse de sédimentation érythrocytaire du sang capillaire par un nouveau procédé

## RÉSUMÉ

On décrit quelques procédés habituels pour déterminer la vitesse de sédimentation érythrocytaire du sang capillaire. On étudie les résultats de Peters (1945) et on décrit une modification de son procédé, qui demandait 0,25 c.c. de sang et 0,05 c.c. de citrate de soude.

La comparaison des résultats de ce procédé, employant du sang capillaire (50 malades) et veineux (30 malades), à ceux qu'on obtient avec la méthode de Westergren, montre que la micro-méthode permet de prévoir précisément, à toutes les vitesses de sédimentation, les chiffres donnés par la méthode de Westergren.

# Determinación de la velocidad de sedimentación eritrocitaria de la sangre capilar por un nuevo método

## SUMARIO

Se describen algunos procedimientos habituales para determinar la velocidad de sedimentación eritrocitaria de la sangre capilar. Se estudian los resultados de Peters (1945) y se describe una modificación de su método, que requería 0,25 c.c. de sangre y 0,05 c.c. de citrato de sodio.

Al comparar los resultados con este método, empleando la sangre capilar (50 enfermos) y venosa (30 enfermos) a los obtenidos con el método de Westergren, se ve que el micro-método permite anticipar con precisión, a todas las velocidades de sedimentación, las cifras que se obtiene con el método de Westergren.

## RELATION BETWEEN THE AFFINITY FOR CONGO RED AND THE GLYCOPROTEIN CONTENT OF SERUM IN RHEUMATOID ARTHRITIS AND RELATED DISEASES\*

BY

BØRGE LARSEN

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Disappearance of congo red from the serum has long been considered by many investigators to be the best and most constant indicator of amyloidosis. The congo red test, as shown by Bennhold (1923), measures the proportion of this dye which is retained in the plasma one hour after its intravenous injection. The validity of this test has been the subject of intense discussion. Disappearance of 40-100 per cent. of the dye from the serum within one hour is generally regarded as a positive test, but according to Stemmerman and Auerbach (1944) and Taran and Eckstein (1942) the test should not be considered positive unless 90-100 per cent. disappears. In an experiment of Dixon, Ramcharan, and Ropes (1955), the congo red test tended towards positivity in 114 out of 227 patients with rheumatoid arthritis. In many cases of primary amyloidosis no affinity for congo red is found (Johansson and Pfeiffer, 1954), and Aegerter and Long (1949) demonstrated a positive congo red test in four out of five cases with systemic lupus erythematosus.

These observations lead to the suggestion that the disappearance of congo red from the serum is due not only to the presence of amyloid in the tissues, but also to other factors. One such possible factor that can be studied is the binding of congo red to the serum. Since congo red does not penetrate semipermeable membranes, equilibrium analysis could not be used in the present study. The method herein devised is based on a partition analysis system. Cellulose powder, which has a great affinity for congo red, was loaded with congo red. Upon shaking this congo red loaded cellulose powder with a buffered serum solution, congo red is taken up by the serum. The dye-binding capacity of serum from patients with rheumatoid arthritis and

related diseases was compared to the serum content of glycoprotein and the results are reported below.

### Material and Methods

A group of 83 sera with a positive streptococcal agglutination titration were kindly furnished by Statens Serum Institute, Copenhagen, where the streptococcal agglutination titrations (S.A.T.) were performed. The control group consisted of twenty sera with negative (S.A.T.), 37 sera from patients with manifest rheumatoid arthritis, and twenty normal sera collected by Dr. Jorgen Kryger. Other sera reported were from the University Hospital of Copenhagen.

**Congo Red Suspension.**—50g. cellulose powder (Schleicher and Schüll, No. 123, from chromatography) are suspended in 200 ml. of a 0.5 per cent. congo red solution in water (Congo red: Grüber and Co.). After stirring for 2 hours, the suspension is filtered and washed with water until the filtrate is colourless. The washed red powder is then suspended in n/20 phosphate pH 7.4.

**Procedure.**—The congo red suspension is diluted 1 : 5 with water. From this diluted suspension 5 ml. are taken with a Krogh syringe during stirring, and to this 5 ml. are added 25  $\mu$ l. serum with a micropipette. A dry serum solution is used as standard for every set of analyses. The test tubes with serum and congo red suspension are shaken together with a blank for one hour at room temperature. After centrifugation, the supernatant is read against the blank in a Beckmann B. spectrophotometer at 525 m $\mu$ . The extinction of the blank read against water should not exceed 0.03. Having set the congo red affinity of normal sera at 100 per cent., the standard dry serum solution was found to be 85 per cent.

**Serum Albumin.**—This was determined by the micro method of Waddell (1956).

**Determination of Serum Glycoproteins.**—Periodic Acid-Schiff (P.A.S.) stainable serum proteins were determined by the method of Laurell and Skoog (1956). The intensity of the eluted fuchsin-sulphite stain of 10  $\mu$ l. serum spots on paper strips coloured by the P.A.S. staining procedure were read at 550 m $\mu$ .

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TABLE I  
MEAN CONGO RED AFFINITY FOR SERUM, SERUM CONTENT OF GLYCOPROTEIN, AND  
SERUM P.A.S. INTENSITY

No. of Sera	Diagnosis	Congo Red Affinity (per cent.)	Protein-bound Hexose (mg. per cent.)	P.A.S. Intensity
83	S.A.T. Positive	83±1.1	184±4.2	195±6.7†
20	S.A.T. Negative	94±2.9	161±8.1	105±9.3‡
35	Rheumatoid Arthritis	80±1.8	183±5.2	174±8.2
19	Controls	104±3.1	114±2.2	85±4.2

† 83 pairs of observations.  
‡ 20 pairs of observations.

CORRELATION COEFFICIENTS BETWEEN CONGO RED AFFINITY AND:

(a) Serum Glycoprotein		(b) P.A.S. Intensity	
Group	r	Group	r
S.A.T. Positive	-0.376*	S.A.T. Positive	-0.407*
S.A.T. Negative	+0.019	S.A.T. Negative	-0.283
Rheumatoid Arthritis	-0.213	Rheumatoid Arthritis	-0.109
Controls	+0.449	Controls	-0.244

\* Statistically significant at the 0.05 level.

**Total Protein-bound Hexose.**—This was determined with anthrone. Using the method of Björnesjö (1955), an accuracy of 2 per cent. is obtained for each determination. The results are expressed in mg. protein-bound non-hexosamine hexose per 100 ml. serum.

### Results

The mean values and corresponding standard errors of congo red affinity and the glycoproteins, determined both as P.A.S. stainable glycoprotein and as total protein-bound hexose, are summarized in Table I for the four groups of S.A.T. positive sera, S.A.T. negative sera, rheumatoid arthritis patients, and controls. It is demonstrated that the mean of the S.A.T. positive group is significantly lower than that of the S.A.T. negative group as regards congo red affinity, and significantly higher than that of the S.A.T. negative group as regards both serum glycoprotein and P.A.S. intensity. Comparison between the groups of sera from patients with rheumatoid arthritis and from the controls gives the same significance.

For the S.A.T. positive group there is a significant negative correlation between congo red affinity values and the corresponding serum glycoprotein values ( $r = -0.376$ ) and also between the congo red affinity values and the corresponding P.A.S. values ( $r = -0.407$ ). For the other three groups the correlations were not significant; indeed, for the control group, between congo red affinity and serum glycoprotein there was a *positive* correlation but it did not attain significance level on such small numbers.

In Fig. 1 the correlation between congo red affinity and serum glycoprotein is shown graphically for eleven S.A.T. positive and eleven S.A.T. negative

sera, selected at random from the two series for illustrative purposes. Where the values expressing the congo red affinity are progressing towards values of

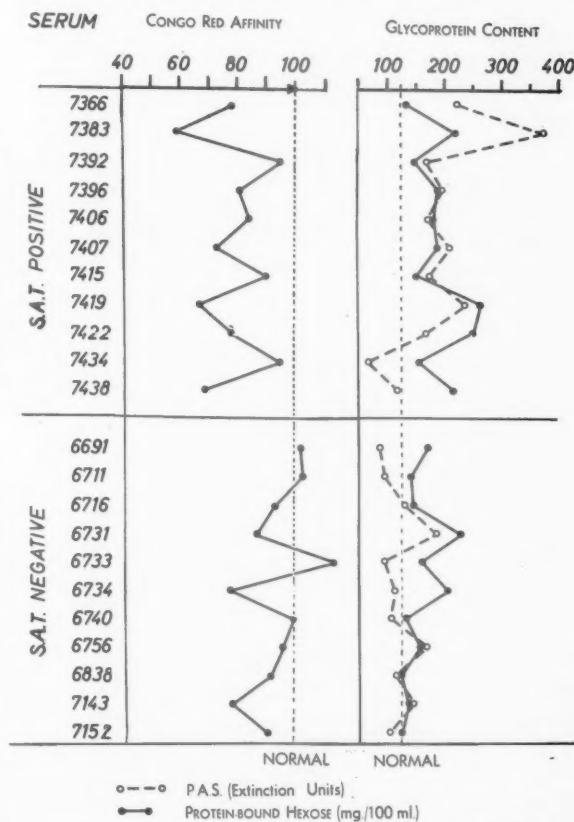


Fig. 1.—Correlation between congo red affinity and serum glycoprotein content in eleven cases with S.A.T. negative sera and eleven cases with S.A.T. positive sera.



100 per cent., *i.e.* where they are tending towards the normal, the total of protein-bound hexose also tends towards the normal, 123 mg./100 ml. serum (Larsen, 1958), and the P.A.S. intensity shows the same fluctuations.

Determinations of congo red affinity were also carried out on sera from four patients with systemic lupus erythematosus, one with proven amyloidosis, and on nine sera from patients with diabetic nephropathy. Table II shows the decreased congo red affinities and the increased serum glycoprotein concentrations in these sera.

TABLE II  
CONGO RED AFFINITY FOR SERUM AND  
SERUM CONTENT OF GLYCOPROTEIN  
IN OTHER SERA

Diagnosis	Subject No.	Congo Red Affinity (per cent.)	Protein-Bound Hexose (mg. per cent.)
Systemic Lupus Erythematosus	I	92	131
	II	55	156
	III	85	165
	IV	61	139
Amyloidosis	Afd. B.	33	196
Diabetic Nephropathy	OL.	69	191
	KT.	75	185
	294	65	164
	296	41	235
	296	42	253
	297	83	213
	298	70	257
	303	78	137
	304	66	192

The result of dividing the sera into groups with increasing congo red affinity and determining the average glycoprotein content in these groups is

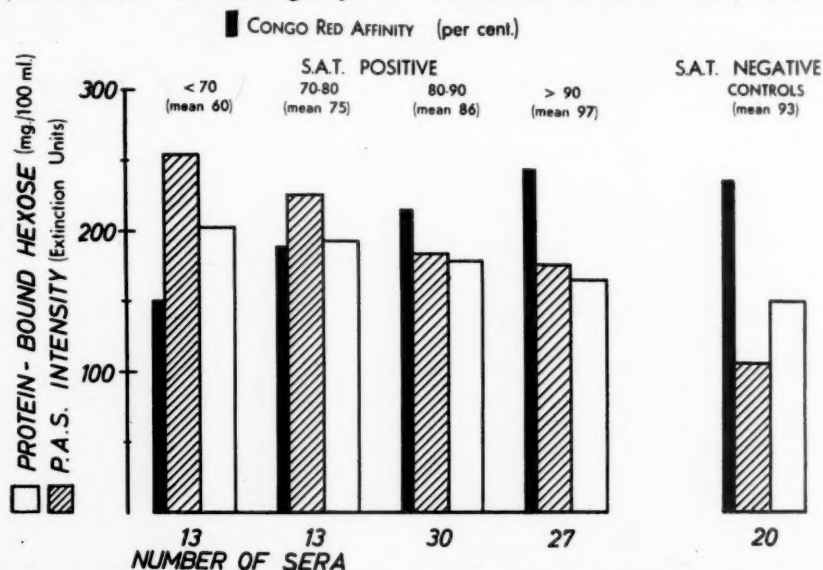


Fig. 2.—Classification of 83 S.A.T. positive sera into four groups of increasing affinity to congo red, showing high serum glycoprotein content in the groups with low congo red affinity and vice versa. The control group is composed of twenty S.A.T. negative sera.

demonstrated in Fig. 2 on the S.A.T. sera and in Fig. 3 (opposite) on sera from patients with proven rheumatoid arthritis. These Figures show an inverse ratio between congo red affinity and the serum content of glycoproteins.

The serum albumin concentration is plotted against the congo red affinity in Fig. 4 (opposite). Here some correlation is demonstrated between the albumin content and the degree of congo red uptake in the serum, but fluctuations in the congo red affinities are greater than the albumin variations.

### Discussion

The comparability of the congo red method *in vitro* with the original Bennhold method *in vivo* is favourable as regards the degree of dye retention in the serum. As shown by Sairanen, Koskinen, and Holopainen (1955), normal subjects exhibit a disappearance of congo red of 33 per cent. and patients with rheumatoid arthritis of 48 per cent. The congo red affinity was lowered by 15 per cent. for patients with rheumatoid arthritis, and by the *in vitro* method this difference was of the same order of magnitude.

Among soluble proteins serum albumin is outstanding in forming reversible complexes with a variety of compounds of known structure, in particular with organic anions (Klotz and Urquhart, 1949). It was therefore thought that the low albumin content seen in the sera investigated could account for the lowered affinity of serum for congo red (Rawson, 1943). The variations in albumin concentrations showed a correlation with the congo

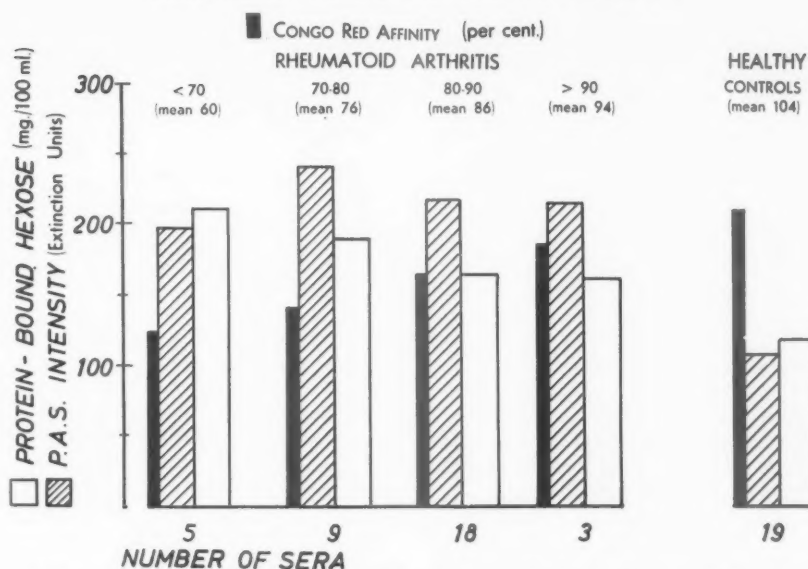


Fig. 3.—Classification of 35 sera from patients with rheumatoid arthritis into four groups of increasing affinity to congo red as in Fig. 2. The control group comprises nineteen sera from healthy subjects.

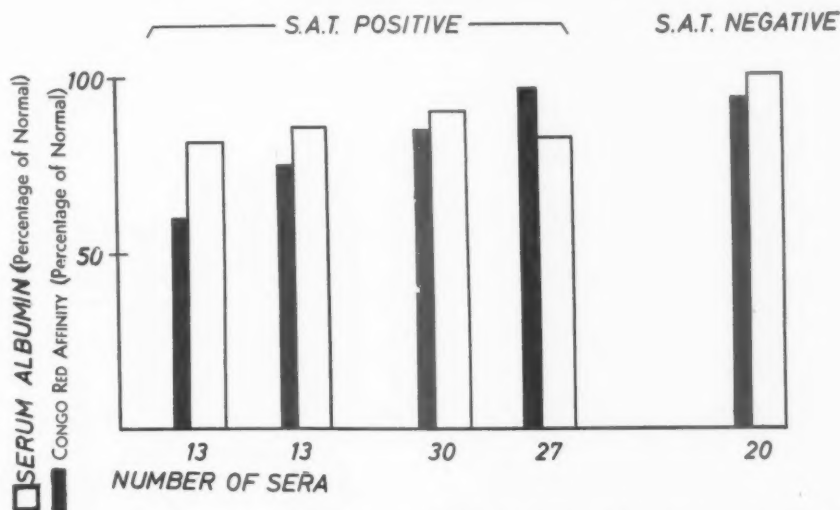


Fig. 4.—Comparison of congo red affinity for serum and serum albumin in groups of increasing congo red affinity, for 83 S.A.T. positive sera and twenty S.A.T. negative sera.

red affinity. While the role of albumin in the binding of congo red cannot be excluded, other factors may also be operative. Organic ions are known to compete with different dye anions in their affinity for serum albumin; for instance, anionic dyes can compete with polysaccharide anions (Klotz, 1953). The same competitive effect may be demonstrated by the *in vitro* distribution method using congo red (Larsen, 1958).

It is therefore probable that the high content of glycoproteins in the serum may suppress the congo red affinity for the serum just as an increased glyco-

protein concentration may reflect an increased concentration of polysaccharide anions.

#### Summary

A new method of determining the congo red affinity of serum has been devised, whereby the distribution of congo red between cellulose powder and serum is estimated.

The congo red affinity of sera from patients with rheumatoid arthritis, lupus erythematosus, diabetic nephropathy, and amyloidosis, was decreased. The serum glycoprotein content of the same sera was

increased and the ratio between congo red affinity and serum glycoprotein content varied inversely.

It is suggested that the decreased congo red affinity for the sera investigated may be due not only to the lowered serum albumin content but also to the competition of congo red with polysaccharide anions.

The author wishes to thank Dr. K. Kalbak who gave him the impetus to start these studies.

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**Relation entre l'affinité pour le rouge Congo et le contenu du sérum en glycoprotéines dans l'arthrite rhumatoïdale et les maladies apparentées**

#### RÉSUMÉ

On a imaginé un nouveau procédé pour déterminer

l'affinité pour le rouge Congo en mesurant sa distribution entre une poudre de cellulose et le sérum.

L'affinité pour le rouge Congo des sérums des malades atteints d'arthrite rhumatoïdale, de lupus érythémateux, de néphropathie diabétique et de dégénérescence amyloïde était diminuée. Dans les mêmes sérums le taux des glycoprotéines se trouvait augmenté, en raison inverse de l'affinité pour le rouge Congo.

On suggère que l'affinité diminuée pour le rouge Congo des sérums étudiés serait due non seulement à un taux d'albumine sérique diminué, mais aussi à la concurrence entre le rouge Congo et les anions polysaccharides.

**Relación entre la afinidad para el rojo congo y el contenido de las glicoproteínas en el suero en la artritis reumatoide y las enfermedades afines**

#### SUMARIO

Se inventó un nuevo método para determinar la afinidad para el rojo congo; este consiste en medir su distribución entre un polvo de celulosa y el suero.

La afinidad para el rojo congo de los sueros de enfermos con artritis reumatoide, lupus eritematoso, nefropatia diabética y amiloidosis se vió disminuida. En los mismos sueros la glicoproteínas se vieron aumentadas en razón inversa de la afinidad para el congo rojo.

Se sugiere que la afinidad disminuida para el rojo congo de los sueros estudiados se debe no sólo a una baja de la albumina sérica, sino también a la rivalidad entre el rojo congo y los aniones polisacáridos.

## BOOK REVIEWS

**Les Collagénoses.** Rapports présentés au XXXIe Congrès Français de Médecine, Paris, 1957. Pp. 246, 10 figs. Masson, Paris. (2,400 Fr. frs; 45s.)

The papers read at the 31st French Congress of Medicine have been grouped into three volumes, the first of which is devoted to the collagen diseases. In discussing the concept of "collagen disease", Delarue, Mignot, and Civatte point out that Klemperer has recently objected to the substitution of terms such as "connective tissue disease" or "mesenchymal disease" since these expressions tend to suggest a cellular rather than an intercellular pathology. The expression "collagen disease" is itself so all-embracing that it may include a very large number of conditions, although, in practice, the clinician has only about four of them in mind. The biology and pathology of collagen is dealt with at some length by Delaunay and Brazin, and dermatological lesions by Dupont, Fiévez, and van Caneghem. Finally, the alleged visceral manifestations of collagen diseases are unravelled by Turiaf, Marland, and Moreau.

The various contributors cover virtually all that is known about the so-called collagen diseases. The bibliography offered to the reader is on a generous scale, but since this volume is likely to be used as a work of reference it is unfortunate that a better method was not used for presenting it.

DAVID PREISKEL

**Klinische Rheumatologie.** By Werner Moll. 1957. Pp. 454, 63 figs, 2 col. illus. Karger, Basel. (Sw. frs 79; £6 10s.)

This is an important textbook on clinical rheumatology in the German language. As Prof. de Sèze remarks in the Preface, the author has treated rheumatology not as a subject in itself but as part of the wider field of general medicine. About 66 pages (of a total of over 400) are devoted to terminology, classification, osteology, and methods of diagnosis and treatment. The same care has been taken in introducing various conditions which merit chapters of their own and such attention to detail often imparts information not readily found in many textbooks on rheumatology as, for example, a list of

muscles involved in carrying out complex movements of the shoulder. Somewhat surprisingly, a separate chapter is devoted to the "fibrositis syndrome"; this is a generic term intended to include such conditions as the painful shoulder and "tennis elbow", but attempts to regard it as an entity with its own aetiology and pathology appear to be half-hearted, as they should be. Perhaps the term "non-articular rheumatism" is a happier choice.

In general, one does not expect to find humour in a book on the rheumatic diseases, but the author's wit if he has any will be revealed in the chapter on gout. In this we are not disappointed; the delightful fable of Lafontaine ("The Gout and the Spider", written in 1668) and other tit-bits help to lighten the reader's burden in grappling with the small, closely set, print which has resulted from compressing a mass of detail into a book of moderate proportions.

The last section contains photographs, x rays, and colour-plates—all of excellent quality. It is fascinating to watch the gradual development of rheumatoid arthritis in hands and feet and to correlate naked-eye appearances with the accompanying x-ray photographs.

The book is provided with a table of contents, an index, and an ample list of references, the last of which would look better if recorded by the Harvard system. Although the book has obvious uses as a work of reference, its main appeal lies in the illustrated section.

DAVID PREISKEL

**Patología de las Pequeñas Articulaciones Intervertebrales** (The Pathology of Diseases of the Intervertebral Joints). By J. M. Vilaseca and P. Barceló. 2nd edition, 1958. Pp. 404, 231 illus. Salvat Editores S.A., Barcelona. (495 pesetas; £3 10s.)

This is a beautifully produced book, profusely illustrated with excellent reproductions of x rays. The anatomy and pathology, and especially the technique and interpretation of the radiology of arthritis of the spine are described, and its differential diagnosis is discussed. Printed in Spanish, it is recommended for all advanced students of rheumatology.

G. D. KERSLEY

## SOCIETÀ ITALIANA DI REUMATOLOGIA

### *Fifth Rome Rheumatology Day, 1958*

This was organized by the Laziale-Abruzzi Section of the Society, whose president is Prof. T. Lucherini, and was under the chairmanship of Prof. L. Villa, of the Milan Medical Clinic. The following principal papers were presented:

PROF. F. DELBARRE (Paris): Current views on gout, its pathogenesis and treatment.

PROF. F. COSTE (Paris): Two cases of an unusual combination of disorders—carpal tunnel syndrome,

chronic stationary polyarthritis, and photodermic manifestations.

DR. G. COSTA-BERTANI (Buenos Aires): "Barré-Lieou syndrome."

PROF. E. GREPPI (Florence) read a challenging paper on "Rheumatic Cephalgias."

These papers were followed by lively discussions and a variety of other interesting contributions, of which 29 figured in the programme.



# EMPIRE RHEUMATISM COUNCIL

## TWENTY-FIRST ANNUAL REPORT

The 21st Annual Report of the Empire Rheumatism Council was presented by the Chairman, Dr. W. S. C. Copeman, at the Annual General Meeting, held on May 7, 1958, at the Ciba Foundation, London, W.1. He congratulated Lord Evans of Merthyr Tydfil, a member of the Advisory Panel, on his elevation to the Peerage, and the Vice-Chairman, Professor Sir Charles Dodds, on his election as Vice-President of the Royal Society, a very rare honour in the medical profession. He announced that the executive committee had regretfully accepted the resignation of Mr. A. G. Timbrell Fisher who was a founder member of the Council and had served as trustee and as a member of the executive committee for many years, and that all members of the Council regretted the retirement after 10 years of the general secretary, Mr. R. Victor Howell, M.B.E.

### FUNDS

When the 10-year programme of intensified research was announced in 1956 it was coupled with an appeal, sponsored by a committee of leading industrialists under the chairmanship of Lord Astor of Hever, for the sum of £250,000. The Council was most grateful to Lord Astor and his colleagues for their support. £175,000 was still needed, but the Council's activities had been much extended with the funds already received, as was shown by the endowment of a second chair of rheumatology, and by the reports\* from the Research Fellows and from the Director of the Mobile Field Unit.

### RESEARCH

**Fellowships.**—Dr. J. K. Norymberski (Sheffield Centre for the Investigation and Treatment of the Rheumatic Diseases) had been engaged for the last 5 years in the field of biochemistry in relation to the rheumatic diseases. Since 1949, when it was found that cortisone and corticotropin had a profound suppressive effect on the symptoms and signs of rheumatoid arthritis, the relationship and function of the adrenal gland to this disease had been of the greatest importance in the research field. This gland

was a highly complex organ and produced a large number of substances, which because of their chemical structure, were called steroids.

For a better understanding of the part played by cortisone in the suppression of rheumatoid arthritis, these steroid substances should be isolated and recognized, and if possible, measured. Dr. Norymberski, by his work in this field, had brought renown to himself and to the Council. In 1953 he developed a means of measuring a large group of these substances in bulk. This opened the way to further research, and he was able to improve and simplify his method so that it became possible to identify certain groups more accurately. This procedure could be carried out, not only in research laboratories, but also in certain hospitals, and in this way, for the first time, the study of patients could be linked with biochemical laboratory research in the rheumatic field. In 1955, this work progressed further and sub-groups of steroids were identified and analysed for the first time.

A step forward in understanding why rheumatoid arthritis often disappeared temporarily during pregnancy was the result of work from Dr. Norymberski's research laboratory. It was found that during pregnancy there was a gradual increase of a particular chemical substance and an even more pronounced increase of a small sub-group which had only recently been identified. These methods of research were reported at the International Meeting of Biochemists in Brussels. In 1956 it was established that the increase of this important and interesting chemical during pregnancy was due, not to an additional out-put by the adrenal gland, but to the fact that it was destroyed more slowly in the body under these conditions.

Already this research was being put to practical use and it was now possible to measure chemically the effect of certain hormone remedies in cases of rheumatoid arthritis. This would lead to a more accurate regime of dosage, with the possible elimination of hitherto unavoidable adverse effects, and to a better understanding of the disease.

Miss I. H. M. Muir had been working under the direction of Prof. Sir George Pickering, at St. Mary's Hospital, London, on a different aspect of the rheumatic problem, namely, the physical properties of the supporting tissues of the body. The so-called "soft-tissues", made up of muscles, ligaments, fat and other connective-tissue structures, were frequently involved in different types of rheumatic disease, and Miss Muir had been studying some of the chemical reactions which take

\* These are printed in full on pp. 34-46 of the Annual Report and may be obtained from the Secretary, Mr. M. G. Andrews, Faraday House, 8-10 Charing Cross Road, London, W.C.2 (Telephone: COVent Garden 0871).

place in connective tissue, both in the normal state and in disease.

Work with atomically-labelled substances whose progress could be followed by a Geiger counter had shown that the rate of destruction of certain elements was accelerated in disease. It was first necessary to work out a method of identifying these substances more accurately, and particular study was made of a chemical, chondroitin sulphate, an integral part of cartilage and other connective tissues.

It was extremely important to isolate this chemical in a pure state, and in 1956 this was achieved.

The discovery that small changes in its chemical structure of this substance resulted in large changes in its physical properties, was a major step forward. Miss Muir had discovered a new type of chemical substance in cartilage which had not previously been identified.

The Council had continued to finance the Chair of Rheumatology at Manchester University and had established a further Research Professorship at London University.

An additional Research Fellow, Dr. Alun Lloyd, was appointed at the University of Wales, University College, Cardiff, to continue studies on chondroitin sulphate.

Dr. Madeline Keech, working on connective tissue under the direction of Professor Tunbridge at the General Infirmary, Leeds, had been studying the action of physical agents and enzymes upon the structure of normal collagen, on the breakdown products of collagen, and on collagen from cases of localized scleroderma.

The Council had also pursued its policy of making grants for promising lines of research, including work on cervical spondylosis by Dr. Marcia Wilkinson under the direction of Sir Russell Brain at the London Hospital, on plasma by Dr. V. Eisen under Professor C. A. Keele at the Middlesex Hospital Medical School, and on the effects of mucopolysaccharides by Dr. P. Fourman at the University of Wales, Cardiff.

In addition, research on steroids by Drs. Robertson and Chapman at the West London Hospital and on plasma by Dr. P. Abelson under Professor E. G. L. Bywaters at Hammersmith Hospital, London, was continued. The Council had supported Professor E. D. Wittkower at Montreal University, Canada, in his research on the psychological aspects of rheumatoid arthritis, and Dr. E. R. Hargreaves in conducting a very useful survey of the prevalence of rheumatoid arthritis in West Cornwall.

Fellowships granted from the Geigy Travelling Fund, had allowed those training in the rheumatic field to gain specialized experience abroad. Dr. Gerald Loewi spent a year in the United States working in the laboratory of Dr. Karl Meyer, College of Physicians and Surgeons, New York, and Dr. L. E. Glynn made a 2-month tour of the United States and Canada and visited many centres of research. Fellowships had been granted to Mr. W. D. Coltart for a short visit to the United States in May, 1958, and to Dr. E. Hess for work under Dr. Morris Ziff at the University of Texas Southwestern Medical School, beginning in September, 1958.

**Clinical Trials.**—Some of the Council's most valuable work was carried out through controlled trials of certain drugs. Such a trial, comparing the effects of cortisone and aspirin, had been undertaken by nine centres throughout the country; the conclusions were that groups of patients treated either with cortisone or with aspirin showed improvement over the 3 years, but that little ultimate objective difference could be detected between the two groups. A further trial of gold therapy in rheumatoid arthritis involving 27 centres was under way.

**Mobile Field Unit.**—This Unit, the only one of its kind in the world, had had a very active year pursuing investigations into geographical, genetic, and industrial factors in relation to various forms of arthritis. With the help of borrowed equipment and temporary staff, several useful surveys had been completed and some interesting results were reported by the director, Dr. J. S. Lawrence.

For geographical studies, standardization of diagnostic criteria was essential. A special committee of the American Rheumatism Association had worked out some valuable clinical criteria, and the Field Unit had developed radiological and serological criteria. Important studies on the standardization of changes seen in x-ray photographs of cases of rheumatoid arthritis and osteoarthritis had been completed by Dr. Lawrence and Prof. Kellgren, the Professor of Rheumatology at Manchester University. At the International Congress on Rheumatism in Toronto, a radiological quiz was organized, to obtain the opinions of sixty physicians from all over the world, so that the standards when published would be truly international.

Dr. Lawrence also took a leading part in an International Conference on Population Studies in Rheumatoid Arthritis held in Bethesda, Maryland, under the auspices of the United States National Institute of Arthritic and Metabolic Diseases and the American Arthritis and Rheumatism Foundation.

The Field Unit had a unique experience of studying random population samples and was becoming an international reference centre, surveys in other countries being increasingly modelled on the technique developed. Dr. Lawrence was also arranging for the interchange of samples of blood and x-ray films taken in other centres so that comparable statistics might soon be available.

Identical surveys were already in progress in Holland, and the Field Unit had been consulted by workers planning surveys in Australia, New Zealand, and Finland. The closest collaboration was also maintained with colleagues in America. Within the United Kingdom there was close co-operation with the Medical Research Council's Pneumoconiosis Research Unit which was conducting medical surveys in South Wales and Scotland. By the end of 1959 the Field Unit surveys in Lancashire and Yorkshire should be complete, and would provide the first accurate figures about the geographical distribution of rheumatoid arthritis and osteoarthritis.

Two genetic studies had been started during the year. The first was producing some unexpected and interesting results, indicating that there might be two forms of rheumatoid arthritis, one with and the other without hereditary characteristics.

Another result which had emerged from the random sample studies was the definition of rheumatoid arthritis of the cervical spine. It had become clear that rheumatoid disease might be present as a disorder of the cervical spine, producing a clinical picture which had not so far been regarded as rheumatoid. This had extended the clinical concept of rheumatoid disease and provided new information for epidemiological studies.

The second genetic study was of the relatives of patients with multiple osteo-arthritis. Preliminary results showed a definite familial trend in this condition.

Industrial surveys were still in the planning stage, but sickness records were being studied in a number of industries with a view to more elaborate investigations of working populations with exceptionally high or low prevalence of rheumatic complaints.

**Equipment.**—A centrifuge had been supplied to Dr. H. West at Sheffield.

Orders had been placed by the University of Manchester for two articulated trailers, a traction Unit, and an estate car, which were being bought with a generous grant of up to £13,000 from the Wellcome Trust. The vehicles would be available for the use of the Field Unit for a survey in Wensleydale, starting in April, 1958. One trailer would be equipped for x ray, including a 120 K.V. set and processing unit, the other as a mobile laboratory with clinical examination room and reception room. The estate car would be used for transporting persons to and from the centre and for carrying portable x-ray equipment for use in the home.

#### EDUCATION

In order to help the medical practitioner, the Council had run annual conferences for consultants, in conjunction with the Postgraduate Medical School of London, Hammersmith. The 1957 Conference took the form of a symposium on rheumatoid arthritis and was fully attended. The Council was very grateful to Professor Sir Francis Fraser, Director of the British Postgraduate Federation, and to Dr. Charles Newman, Dean of the Postgraduate Medical School, who made the course such a great success.

**International Congress.**—The outstanding event of the year was the IX International Congress on the Rheumatic Diseases organized at Toronto by the Canadian Arthritis and Rheumatism Society under the auspices of the International League against Rheumatism, which was attended by 1,200 physicians and surgeons from 44 countries.

**Handbooks.**—For patients the Council had continued to publish and distribute to doctors its two handbooks, on *Rheumatoid Arthritis* and *Osteo-Arthritis*. Many thousands of copies were requested each year from practitioners all over the world and the handbooks would therefore continue to be made available as required.

**Films.**—Through the generosity of Messrs. Lloyd Hamol, a valuable documentary film had been made

for the Council, entitled "One Man's Challenge". This told the story of a man's fight to lead a useful life in spite of being almost completely crippled by rheumatoid arthritis. The film had a very successful "première" in London, was shown at the Harrogate Festival, and had since been seen by many thousands. It had also been chosen by the British Council to be shown overseas and had been given a special award by the British Medical Association. Copies were available from the Council's headquarters for private or public performance.

The Council had also obtained a copy of the Canadian Arthritis and Rheumatism Society's excellent colour film, "Never Surrender".

**Grants.**—The Council had continued to support the Heberden Society, which existed for the advancement of the study of the rheumatic diseases. Meetings, lectures, and demonstrations were held regularly throughout the year and the annual Heberden Oration was given by Professor R. E. Tunbridge, Chairman of the Council's Scientific Co-ordinating Committee, on "The Connective Tissue System".

The Council also renewed its grants to the Libraries of the British Medical Association and the Royal Society of Medicine for the purchase of books on rheumatism and arthritis. The Council's activities had continued to be reported in the *Annals of the Rheumatic Diseases*, which circulated throughout Europe and North America.

#### COMMONWEALTH

The Council continued to keep closely in touch with its affiliated autonomous branches in the Commonwealth.

**Canada.**—The National President of the Canadian Arthritis and Rheumatism Society, Mr. B. H. Rieger, had written as follows:

The past year has witnessed continued growth in the quantity and quality of the services of the Canadian Arthritis and Rheumatism Society.

Our satisfaction that an increased number of patients has been served (6,784 in 1955, and 7,486 in 1956) and that research and other activities have been extended must be tempered by a realization that last year's rate of growth was less rapid than in previous years. This may be ascribed to the emergence of two major problems: a chronic and nation-wide shortage of professional workers, particularly physiotherapists; and the relatively greater unit cost of services provided in smaller towns and rural areas.

The shortage of physiotherapists appears likely to correct itself in the long run. Particularly commendable are the efforts of the British Columbia and Ontario Divisions in co-operating with other groups and authorities to foster the establishment of additional facilities for the professional training of physiotherapists.

While the extraordinary efforts of many voluntary boards and committees are constantly extending the frontiers of the Society's operations, the movement to prevent or correct disabilities due to arthritis among fellow citizens in small towns and rural areas will not likely develop at a rate comparable with the urgency of the need until this situation is generally recog-



nized by provincial governments, and until the principle of philanthropic responsibility towards their economic hinterlands is generally recognized in the larger cities.

Under the stimulus of the research programme instituted by this Society in 1950, interest in arthritis research has grown rapidly in university departments and laboratories throughout Canada. The time has come to capitalize upon the consequent increases in skilled personnel and facilities through a sharp increase in the level of the Society's support for arthritis research, and it is to be hoped that this will be accompanied by an appropriate increase in the arthritis research activities of the Federal Government.

While I have emphasized several of the problems now facing the Society, I believe that its activities will give solid satisfaction to the many thousands who have contributed so generously of their time, money and effort to make possible the excellent results already achieved.

**Australia.**—The Australian Rheumatism Council reported an active year, the highlight of which was the attendance of many members of the Council at the International Congress on Rheumatic Diseases at Toronto. The Council had also published a report on

the survey of rheumatic complaints which was carried out in Sydney in October, 1956. At the first annual meeting of the newly-formed Australian Rheumatism Association, held in October, 1957, papers conveying the scientific advances reported at the Toronto Congress were read, and the following matters were discussed: a library, a fund for special study, provision of funds for research, and the undertaking of some special project to be co-ordinated in clinics throughout Australia.

A week-end course in rheumatic diseases was held in Sydney under the auspices of the Post-Graduate Committee in Medicine in the University of Sydney, and postgraduate instruction of a similar nature was included in courses arranged in other States by the appropriate Post-Graduate Committees.

In its report the Council recommended that funds for medical research and other work were urgently needed, that the establishment of State Divisions should assist in the campaign against rheumatism, and give the support necessary for the establishment of Arthritis Clinics, and that the provision of surgical aids, drugs, etc., to sufferers lay within the province of the Council.

## HEBERDEN SOCIETY

### ANNUAL REPORT, 1957

The President recorded with pleasure the honour of a peerage conferred by Her Majesty the Queen on Sir Horace Evans.

The President expressed to Mr. Victor Howell the great regret felt by all members on his retirement. He had been secretary of the society as well as of the Empire Rheumatism Council for over 10 years and during that time had endeared himself to all members. His remarkable charm and ability had enabled him to deal with the most difficult issues unruffled. It was largely due to him that the Council and the Society had thrived so well during his time as Secretary and his genius for organization had proved invaluable. His retirement was universally regretted, but it was hoped that members will continue to see him from time to time. On behalf of the Society the President, amidst great applause from all those present, presented Mr. and Mrs. Howell with an engraved silver salver as a token of their admiration and friendship.

The following new members had been elected:

**Ordinary Members:** Dr. O. Janus, Dr. B. E. W. Mace, Dr. J. Shulman.

**Associate Members:** Dr. E. V. Hess, Dr. G. Loewi, Dr. A. J. Popert, Dr. Ifor Williams, Dr. V. Wright.

**Overseas Member:** Dr. M. Jeffrey.

The following member resigned during the year:

Dr. S. C. Milazzo (from temporary overseas membership).

The total ordinary membership on January 1, 1958, was 100 and the associate membership 18.

#### Activities

At the invitation of Dr. A. T. Richardson, the first clinical meeting of the year was held at the Royal Free Hospital on February 22, 1957 (*Annals*, 16, 254). Cases and papers, presented by Dr. A. T. Richardson, Dr. J. H. Jacobs, and Mr. R. L. Markham, and Dr. E. V. Hess (*Royal Free Hospital*), were followed by demonstrations by Dr. R. P. Hickey, Dr. A. Beardwell, Dr. A. G. Beckett, and Dr. C. Feldman.

A clinical meeting held on October 18, 1957, at the Wellcome Foundation, London (*Annals*, 16, 516), consisted of a symposium on the IX International Congress of Rheumatic Diseases at Toronto, with contributions from Dr. H. F. West (*Sheffield Centre*), Dr. F. Dudley Hart (*Westminster Hospital*), Dr. A. G. S. Hill (*Stoke Mandeville Hospital*), Dr. R. M. Mason (*The*



London Hospital), and Dr. J. Glyn (*Prince of Wales Hospital*). In addition, a paper was presented by Dr. Harry Coke (*London*).

The Heberden Round, conducted by Dr. J. J. R. Duthie at the Northern General Hospital, Ferry Road, Edinburgh, on May 16, 1957 (*Annals*, 16, 391), was followed by laboratory demonstrations and the presentation of papers by Dr. J. J. R. Duthie, Dr. J. Richmond, Dr. W. R. M. Alexander, Dr. S. C. Milazzo, Dr. L. M. H. Roy, Dr. D. L. Gardner, Dr. J. L. Potter, and Dr. R. J. G. Sinclair (*Edinburgh*). That evening members attended a dinner held in the Albyn Rooms, Edinburgh.

The Heberden Oration for 1957 was delivered on December 13 by Prof. K. Brøchner-Mortensen, of the University Hospital at Copenhagen, on "Gout" (*Annals*, 17, 1). The Orator was presented by the President with the Heberden Medal for 1957.

The Annual Dinner was held on December 13, by kind permission of the Master, at the Hall of the Worshipful Society of Apothecaries, London. Among the guests present were Mr. R. Thompson (Parliamentary Secretary, Ministry of Health), Sir Henry Dale, Sir Harry Platt, Prof. Brøchner-Mortensen, Dr. Hugh Clegg, and Dr. T. F. Fox.

The Annual General Meeting was held on December 13 and 14 at the Wellcome Foundation, London. At the clinical meetings which followed (*Annals*, 17, 120), papers were presented by:

- Dr. B. M. Ansell and Dr. E. G. L. Bywaters (*Postgraduate Medical School, London*): "Joint Manifestations Associated with Ulcerative Colitis";
- Dr. J. S. Lawrence (*Manchester*): "Rheumatoid Family Survey";
- Dr. J. Sharp, Mr. D. W. Purser, and Dr. J. S. Lawrence (*Manchester*): "Rheumatoid Arthritis of the Cervical Spine";
- Dr. J. Ball (*Manchester*): "Pathology of the Rheumatoid Cervical Spine";
- Mr. C. E. Drew (*London*): "An Operation to relieve Thoracic Rigidity in Ankylosing Spondylitis";
- Dr. B. Cruickshank (*Glasgow*): "Heart Lesions in Rheumatoid Disease";
- Dr. B. M. Ansell, Dr. I. Doniach, and Dr. E. G. L. Bywaters (*Postgraduate Medical School, London*): "Aortic Lesion of Ankylosing Spondylitis";
- Dr. Malcolm Thompson (*Newcastle-upon-Tyne*): "Some Observations on Plasma Ascorbic Acid, Dehydro-ascorbic Acid, and Caeruloplasmin Levels in Rheumatoid Arthritis";
- Dr. E. J. Holborow and Dr. D. M. Weir (*London*): "A Factor in L.E. Cell Positive Sera showing Specific Affinity for Tissue and White Cell Nuclei as shown by the Coons Technique";

Dr. George Will (*Glasgow*): "Treatment of Rheumatic Fever with Phenylbutazone".

### Grant-in-Aid

The Society acknowledged with appreciation the renewal of a grant from the Empire Rheumatism Council.

### Library

The Society was indebted to the Ciba Foundation for their kindness in housing the Library at 41 Portland Place, London, W.1.

The Hon. Librarian reported that several additions had been generously presented by the Wellcome Trustees or by Members, the two 16th-century volumes on gout being particularly notable.

He hoped that anyone who had books on rheumatism and arthritis published before 1914 or Heberden relics of any type would be kind enough to bear in mind the needs of the Library.

He thanked those who had already presented volumes and especially Dr. F. Poynter, Librarian of the Wellcome Historical Medical Library.

The following additions had been made in 1957:

*Presented by the Trustees of the Wellcome Medical Foundation:*

- KRAUTERMANN, V. Das Achzende Hufft-Ruck. (on rheumatism, particularly lumbago). 1746.
- KNOTT, J. F. On the Use of Certain Organic Acids in the Gouty, Rheumatic and Allied Diatheses. 1888.
- NIVET, A. Dissertation sur l'hystérie rhumatitante et métastatique. 1806.
- EBSTEIN, W. Die gicht des chemikers Jacob Berzelius. 1904. (on the medical history of Berzelius and a few other eminent medical men who suffered from gout).
- GALES, J. C. Memoirs and Reports on the Efficacy of Sulphurous Fumigation in the Treatment of Diseases of the Skin, Joints and Glandular System. Chronic Rheumatism, Gout, etc. (from the French by Rees Price, M.R.C.S.). 1818.
- BOSCIUS, J. L. Kurtzer Bericht von dem Podagra. 1582.
- ANHART VON GRAETZ, E. Consilium podagricum das ist wie Man sich vor dem Podagra. 1581.
- FELTMANN, G. De dea podagra liber singularis. 1693. (a little known treatise on gout, history of the disease and various methods of treatment).

MOELLENBROCK,

V. A. De varis seu arthritide vaga scorbutica tractatus. 1672.  
(on arthritis with particular reference to wandering gout and scurvy).

MUSGRAVE, W.

De arthritide anomala sive interna dissertatio. 1707.

FALCONER, W.

Observations on Dr. Cadogan's Dissertation on the Gout and all Chronic Diseases. 17??.

LIGER, M. C.-L.

Traité de la goutte. 1753.

COSTE, M.

Traité pratique de la goutte. 3rd ed. 1768.

NISBET, W.

Medical Guide for the Invalid to the Principal Watering Places of Great Britain. 1804.

HOOD, P.

A Treatise on Gout, Rheumatism and Allied Affections. 1st ed. 1871.

BALLONII, G.

De virginum et mulierum morbis. 1643.

*Presented by Dr. W. S. C. Copeman:*

CHEYNE, G.

An Essay of the True Nature and Method of Treating the Gout. 4th ed. 1722.

# OFFICERS FOR 1958

## President:

Prof. J. H. Kellgren, F.R.C.P., F.R.C.S.,  
Rheumatism Research Centre, Clinical Sciences Building,  
York Place, Manchester, 13.

## President-Elect:

Dr. F. Dudley Hart, F.R.C.P.

## Hon. Treasurer:

Dr. F. Dudley Hart, F.R.C.P.,  
Westminster Hospital, London, S.W.1.

## Senior Hon. Secretary:

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## Junior Hon. Secretary:

Dr. A. St. J. Dixon, M.R.C.P.,  
Department of Medicine, Postgraduate Medical School  
of London, Hammersmith Hospital, London, W.12.

## Hon. Librarian:

Dr. W. S. C. Copeman, O.B.E., F.R.C.P.,  
41 Harley Street, W.1.

## Hon. Auditor:

Wilfred G. Wilks, Esq., F.C.C.S., F.R.Econ.S.

## General Secretary:

M. C. G. Andrews  
(Tel. No.: COVent Garden 0871.)

## PROGRAMME FOR 1958

Heberden Round at Leyden, Holland, in April,  
conducted by Prof. J. Goslings.

Clinical Meeting on October 10.

Heberden Oration, Annual General Meeting, and  
Dinner in December. Date and venue to be  
notified later.

Titles and short programme notes of original communications which members wish to make to the Society during 1958 should be sent to the Senior Hon. Secretary at least one month before the date of the meeting. Abstracts for publication in the *Annals of the Rheumatic Diseases* (approximately 300 words) should be sent in advance or handed to the secretary at the meeting. Additional meetings will be arranged if necessary.

**Clinical Meeting.**—The following papers were read at a meeting held in the Meyerstein Theatre of the Westminster Medical School on February 14, 1958.

**Value of Uricosuric Agents and in particular of G.28315 in Gout,\*** by G. D. Kersley, E. R. Cook, and D. C. I. Tovey (Rheumatism Research Unit, Royal National Hospital for Rheumatic Diseases, Bath).

**Clinical Experience with a New Phenylbutazone Analogue.** By D. M. Burley (Westminster Hospital): The metabolite of phenylbutazone, p-hydroxy phenylbutazone isolated by Burns, Rose, Goodwin, Reichenthal, Horning, and Brodie (1955) and designated G.27202 by Pfister and Hafliger (1957), had been reported by Brodie, Burns, Paton, Steele, Yü, and Gutman (1956) to have a similar antirheumatic, but more potent uricosuric, effect than phenylbutazone itself. G.27202 was a more potent anti-inflammatory and antipyretic agent in animals, and in man its gastric toxicity was less than that of phenylbutazone although other toxic manifestations were similar. After intravenous injection in man half of it disappeared from the plasma in 48 hours.

At the Westminster Hospital Rheumatism Department, G.27202 was compared with phenylbutazone as regards the reduction of pain and stiffness and the frequency of gastric intolerance in rheumatoid arthritis and ankylosing spondylitis. G.27202 was substituted for phenylbutazone, dose for dose (usually 200 to 400 mg. daily), for from 5 days to several weeks in 72 patients. The results may be summarized as follows:

## Relief of Pain

9 patients found G.27202 more effective than phenylbutazone.

\* To be published in full in the September issue of the *Annals*.

23 patients found phenylbutazone more effective than G.27202.

18 patients considered them equally effective.

22 patients found neither effective or the effects variable.

#### Gastric Intolerance

56 patients showed no gastric intolerance to either compound.

16 patients showed no gastric intolerance to phenylbutazone.

(Of these sixteen patients, eight showed gastric intolerance to G.27202, although in four this was only slight.)

It was concluded that G.27202 was less effective than phenylbutazone in relieving pain and stiffness in these conditions, but had approximately half the gastric toxicity. Further trials were recommended.

#### REFERENCES

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**Rheumatoid Polyarthritis Association with a Negative Sheep Cell Agglutination Test. A Follow-up Study.** By A. St. J. Dixon (*Postgraduate Medical School, Hammer-smith*): This study concerned all in-patients of the Rheumatism Research Centre at the Manchester Royal Infirmary, who had an active and progressive polyarthritis with a raised erythrocyte sedimentation rate and negative sheep cell agglutination test (S.C.A.T.), and in whom no diagnosis relevant to the polyarthritis other than rheumatoid arthritis (R.A.) was made.

Of 64 such patients, six had died and 51 were seen again after an average of 5 years, when thirteen patients had developed a positive S.C.A.T., most of whom had a distribution of arthritis typical of R.A. and half of whom had developed nodules. Eighteen had typical R.A. and a negative S.C.A.T.; none of these had subcutaneous nodules but most of them had flexor tendon lesions in

the hands. Fifteen had an atypical distribution of arthritis and negative S.C.A.T. without nodules or flexor tendon lesions of any sort. Eleven had developed confirmed or probable polyarthritic diseases other than R.A., including psoriatic arthritis, reticulohistiocytosis, myelomatosis, generalized osteo-arthritis, and gout.

The following conclusions were drawn:

- (1) That other diseases may simulate rheumatoid arthritis very closely and a negative S.C.A.T. may alone indicate the difference.
- (2) That there is a group of patients with severe polyarthritis which does not fit the clinical and serological picture of R.A. requiring further study.
- (3) That a negative S.C.A.T. is compatible with severe or fatal diseases in otherwise typical R.A.
- (4) That there was no difference in prognosis in patients with typical R.A. between those whose S.C.A.T. was initially negative and later positive, and those in whom the S.C.A.T. was negative throughout. It was amongst the fifteen patients with a negative S.C.A.T., who also had atypical R.A., that some of the severest illnesses and most dramatic remissions were found.

The following cases were shown:

**Neuropathic Changes in Rheumatoid Arthritis.** By Dr. J. R. Golding and Dr. D. H. Mackenzie.

**Disseminated Lupus Erythematosus on High Dosage of Prednisolone with Spontaneous Intussusception of the Intestine.** By Dr. J. R. Golding.

**Ankylosing Spondylitis in a 60-year-old Male who had never had Spinal Symptoms.**

**Rheumatoid Arthritis in a Woman who went into Immediate Remission after Electrocution and the loss of Three Fingers and had remained in Remission for over 2 years.** By F. Dudley Hart.

**Reiter's Disease.** By Dr. Denis Burley.

## ABSTRACTS

This section of the ANNALS is published in collaboration with the two abstracting Journals, ABSTRACTS OF WORLD MEDICINE and OPHTHALMIC LITERATURE, published by the British Medical Association.

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Pararheumatic (Collagen) Diseases; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with research into the scope and modus operandi of steroid therapy.

### Acute Rheumatism

**Controlled Study of Three Methods of Prophylaxis against Streptococcal Infection in a Population of Rheumatic Children. I. Streptococcal Infections and Recurrences of Acute Rheumatic Fever in the First Two Years of the Study.** WOOD, H. F., STOLLERMAN, G. H., FEINSTEIN, A. R., HIRSCHFELD, I., RUSOFF, J. H., TARANTA, A., HAAS, R. C., and EPSTEIN, J. A. (1957). *New Engl. J. Med.*, 257, 394. 23 refs.

It is established that recurrences of rheumatic fever can be prevented in a high proportion of cases by anti-streptococcal prophylaxis. A preliminary investigation was carried out at Irvington House, Irvington-on-Hudson, New York, with the twofold object of determining the comparative efficacy of three different prophylactic regimens and observing the natural history of rheumatic heart disease in the presence of continuous prophylaxis over a period of 5 years. The three regimens were:

- (1) sulphadiazine, 1 g. a day by mouth in a single dose;
- (2) penicillin, 200,000 units a day by mouth in a single dose half-an-hour before breakfast;
- (3) benzathine benzylpenicillin, 1,200,000 units in 2 ml. by intramuscular injection every 4 weeks.

A total of 405 children, all of whom had had a definite attack of rheumatic fever within the preceding 28 months, were divided into eight groups: those without heart disease were divided into age groups 5 to 9 and 10 to 15 years and each age group was then subdivided into those who had been free from rheumatic activity for 3 to 4 months and those who had been free for 15 months or more; patients with heart disease were assigned to four similar groups. By a random allocation of patients to a prophylactic agent it was ensured that there were three treatment groups of approximately equal size in each of the eight groups. Each patient was seen once a month, throat swabs for culture being taken at each visit and blood for serological examination being obtained every other visit.

The results obtained in the first two years of the study, 1954 to 1956, showed that 1,200,000 units of benzathine penicillin administered intramuscularly every 4 weeks was more effective in preventing both streptococcal infections and recurrences of rheumatic fever than either of the other two prophylactics. The authors suggest that one reason for this superiority is that injection ensures that the drug is received, whereas there is no certainty that the patients take the drugs by mouth.

Kenneth Stone.

**Paradoxical Values of the Erythrocyte Sedimentation Rate in Rheumatic Fever: a Comparison among Three Acute Phase Tests.** HARRIS, T. N., FRIEDMAN, S., and TANG, J. (1957). *Amer. J. med. Sci.*, 234, 259. 2 figs, 32 refs.

The relative values of the erythrocyte sedimentation rate (E.S.R.) and the serum levels of C-reactive protein (CRP) and mucoprotein (MPT) as indices of activity in rheumatic fever under conditions in which the E.S.R. is known to be fallacious were investigated at the University of Pennsylvania School of Medicine, Philadelphia. In seven children with acute rheumatic carditis and cardiac failure the E.S.R. was initially within normal limits and increased with recovery, whereas the serum CRP level was maximal in the most acute phase and fell steadily thereafter. On the other hand, the behaviour of the serum MPT level was similar to that of the E.S.R. In fourteen patients receiving hormone therapy the E.S.R. fell rapidly to normal only to show a marked "rebound" when treatment ceased. The response of the serum CRP level was similar, but the serum MPT concentration was only slightly affected by treatment. Of two patients with sickle-cell trait and acute rheumatism the E.S.R. was normal in one and slightly raised in one, but the CRP and MPT values were markedly abnormal in both. Finally, in a group of eleven adolescent children in whom the E.S.R. remained slightly raised after all other evidence of acute rheumatic fever had subsided, the serum CRP and MPT levels were within normal limits.

C. Bruce Perry.



**Acute Rheumatic Fever in Children. A Comparison of Six Forms of Treatment in 200 Cases.** ILLINGWORTH, R. S., LORBER, J., HOLT, K. S., RENDLE-SHORT, J., JOWETT, G. H., and GIBSON, W. M. (1957). *Lancet*, 2, 653. 14 refs.

The authors here analyse their total experience during the past 9 years at the Children's Hospital, Sheffield, of six different forms of treatment for rheumatic fever. Altogether 200 children were studied. Of these, 145 were included in various controlled studies—55 in a comparison of the effects of bed rest alone and salicylates, seventeen in the Anglo-American co-operative comparison of salicylates in low dosage with corticoids, thirty in a comparison of cortisone plus salicylates in high dosage with salicylates alone in high and low dosage, and 45 in a comparison of cortisone plus salicylates in high dosage with cortisone plus salicylates in low dosage and with cortisone alone. The remaining 55 were extra cases which had been treated during the same period by the same methods, but had not been included in the main series.

As judged by the rate of fall of the erythrocyte sedimentation rate, treatment with cortisone plus salicylates in high dosage was the most effective method used; cortisone given alone or with salicylates in low dosage was more effective than treatment with salicylates only, which in turn gave better results than were obtained with no specific treatment; there was no difference between the effects of salicylates in high and low dosage. The duration of the arthritis was least in the groups receiving cortisone, and was less in those receiving salicylates alone than in those receiving no specific treatment. New rheumatic manifestations developed in none of the cortisone-treated cases, in six of the 77 patients receiving salicylates only, and in nine of the 42 given no specific treatment. Systolic or diastolic murmurs developed less frequently in children receiving cortisone, with or without salicylates, than in the rest, and a higher proportion of the cortisone-treated children than of the others who developed murmurs ultimately lost them. The importance of early treatment was apparent, as only two out of eight cortisone-treated children who had been admitted after 30 or more days' illness lost their murmurs compared with twenty out of thirty so treated who had had symptoms for less than 30 days on admission.

It is concluded that cortisone combined with salicylates in high dosage is the most effective of the various methods of treatment of rheumatic fever studied. (There is a detailed statistical addendum.) C. Bruce Perry.

**Observations on an Epidemic of Streptococcal Infections and Recurrences of Rheumatic Fever among Children treated with Penicillin.** MARKOWITZ, M. (1957). *Pediatrics*, 20, 257. 22 refs.

Observations concerning the dosage of penicillin required to prevent recurrences of rheumatic fever are reported from Johns Hopkins School of Medicine, Baltimore. The study was carried out in a children's convalescent home, in which were 33 children who were convalescent from acute rheumatic fever, during the course of an epidemic of streptococcal pharyngitis.

Each of the rheumatic children received a single daily prophylactic dose of 200,000 units of benzathine penicillin by mouth. In spite of this, however, eleven of them developed Group-A streptococcal infections, indicating that the dosage was inadequate. It is suggested that at least double this dosage of penicillin should be given to such susceptible children in a closed community.

The infected rheumatic children were treated with penicillin in various dosages and four of them, who received a single intramuscular injection of 600,000 units of benzathine penicillin, developed a recurrence of rheumatic fever. It is therefore suggested that this dosage is inadequate for the prevention of rheumatic fever in a susceptible subject who develops a streptococcal infection. [This is an important paper.]

R. S. Illingworth.

**Observations on Serum Lipid Levels in Rheumatic Subjects and Their Siblings.** CHANG, I., COBURN, A. F., and PARGELLIS, P. P. (1957). *Amer. J. med. Sci.*, 234, 78. 16 refs.

It has been reported that in patients with rheumatic fever the serum phospholipid level is low, and one of the present authors showed (Coburn, *Amer. J. Dis. Child.*, 1945, 70, 339) that feeding large amounts of whole egg-yolk powder prevented recurrence of rheumatic fever. At the Rheumatic Fever Research Institute, Chicago, the serum total lipid, phospholipid, and cholesterol levels were determined over a period of 2 years in a group of 34 rheumatic fever patients, and in a smaller group of the siblings of these patients who were without rheumatic disease. In addition, the rheumatic-fever group received an alcohol-soluble extract of egg-yolk, the equivalent of two to three egg-yolks a day being consumed over the period of the trial. Fasting venous blood samples were obtained from the rheumatic patients when they were receiving their usual diet and again after a period of supplementary egg-yolk.

Two methods of lipid extraction were used; in the first year the method followed required prolonged boiling, which was thought to decompose lipid; in the second year the method of Skerry and Warren was employed. The serum total lipid and cholesterol levels were significantly lower before treatment in the rheumatic fever group than in the controls. After egg-yolk was added to the diet the serum total lipid, cholesterol, and phospholipid values rose, but little increase was seen after 3 months. [These findings are difficult to evaluate because of the change in methods and because the possible effects of seasonal change are not discussed.]

E. G. L. Bywaters.

**Rheumatic Fever in the Aged. Report on a Hospital Series from Oslo.** [In English.] KJÖRSTAD, H. (1957). *Acta med. scand.*, 158, 337. 2 figs, 16 refs.

It is first pointed out that during the last 50 years the incidence of rheumatic fever in Scandinavian countries has tended to decline. A table giving the number of notified cases of the disease per 10,000 inhabitants in Helsinki, Oslo, and Copenhagen at various dates in the

last 75 years shows that there has been a pronounced fall—for example, the notification rate in Oslo was 0.4 per cent. in 1885 and 0.014 per cent. in 1951-55.

A study is then reported of the incidence of rheumatic fever in elderly subjects, based on the total number of patients with a diagnosis of acute rheumatism or rheumatic fever discharged from Ullevål Hospital, Oslo, over the period 1923 to 1927 (283 such patients) and over the 10-year period 1946 to 1955 (298 patients). These cases were analysed by age and sex, a series recorded from the same hospital between 1895 and 1907 being used for purposes of comparison. A considerable change in age distribution was observed, the mean age in the three periods 1895-1907, 1923-27, and 1946-55 being respectively 25.8, 27.0, and 29.7 years for men, and 26.7, 28.4, and 35.9 years for women. This coincided with a shift towards older age groups in the general population of Oslo, and in the period 1946-55 the age distribution of patients with rheumatic fever accorded closely with that in the city population. In the 5-year period 1951-55, 25.7 per cent. of rheumatic fever patients were over 50 years of age (27.7 per cent. of the city population), whereas in 1923-27 only 6 per cent. (18.8 per cent. of the city population) were over this age. The shift in age distribution was predominantly among females.

Of 46 patients over the age of 50 (seven of them over 70) who were discharged between 1946 and 1955, seventeen had a history of previous attacks of rheumatic fever or pre-existing heart disease—a proportion considerably higher than that in a control group of patients without rheumatic fever discharged during the same period. Discussing the clinical findings in these 46 patients, the author states that fever (38° C. for 2 days) occurred in 32, the erythrocyte sedimentation rate was above 20 mm. per hour in all except one, and 34 had polyarthritis. There were, however, pre-existing chronic joint lesions in fifteen patients, and in at least four chronic rheumatism persisted after discharge. Carditis was present in fourteen (eleven of whom had no previous history of the condition); this was revealed by changes in the electrocardiogram in twelve, only two of the patients having clinical pericarditis. In 33 of the 46 patients the diagnosis accorded with the criteria laid down by the American Heart Association. *E. G. L. Bywaters.*

**Cortisone Treatment of Rheumatic Fever. Relationship of Weight to the Speed of Fall of Erythrocyte Sedimentation Rate.** ILLINGWORTH, R. S., JOWETT, G. H., and GIBSON, W. M. (1957). *Lancet*, 2, 659. 2 refs.

In this study from the University of Sheffield, the rates of fall of the erythrocyte sedimentation rate (E.S.R.) during treatment for rheumatic fever with cortisone (with or without salicylates) in children in different states of nutrition, as assessed from the weight in relation to age, are compared. Children who were 10 per cent. or more above the average weight for their age were classed as "over-weight", and those who were 10 per cent. or more below the average as "underweight", the average figures used being those given by Gore and Palmer (*Lancet*, 1949, 1, 385; *Abstr. Wld Med.*, 1949, 6, 48).

Of eighteen overweight children, only 33 per cent. had a normal E.S.R. by the 15th day of treatment, whereas among thirty underweight children the proportion was 73 per cent. and among 31 of average weight it was 55 per cent. Significant differences between overweight and underweight children were not observed in a similar study of patients treated with salicylates alone.

*C. Bruce Perry.*

**Systolic Murmurs in Healthy Children and in Children with Rheumatic Fever.** LESSOF, M., and BRIGDEN, W. (1957). *Lancet*, 2, 673. 2 figs, 10 refs.

A clinical and phonocardiographic study of 100 healthy children aged 3 to 14 years and 200 children [age range not specified] with rheumatic fever. Phonocardiograms were recorded with a multi-channel cathode-ray phonocardiograph from fifty of the healthy children and 150 of those with rheumatic fever.

A systolic murmur was heard in 96 of the healthy children. In 71 it was short, soft, and loudest over the pulmonary area or left sternal edge. In twenty cases the murmur was heard over a wider area of the praecordium, but in only five was it loudest at the apex. In only five cases was the murmur even moderately loud and three of these children had considerable chest deformity. Phonocardiograms showed that these murmurs were not of a uniform frequency, that their onset was often delayed after the first sound, and that they always ended before the second sound began.

In all 200 children with rheumatic fever a systolic murmur was heard, and in most cases it was loud. In 33 of the 100 patients seen in the first attack the murmur was short and indistinguishable from the type heard in the normal children; in 31 the systolic murmur was also within the normal range, but was associated with a diastolic murmur, so that carditis was indicated; and the remainder had an apical murmur filling the whole of systole. Of the 100 children who had had more than one attack of rheumatic fever, nine had a systolic murmur indistinguishable from that heard in the normal group and 27 had a similar murmur with an associated diastolic murmur. The remaining 64 children had pansystolic murmurs as well as diastolic murmurs. In twelve cases a pansystolic murmur heard during the acute phase disappeared on recovery, leaving only a soft basal or a short apical murmur.

It is concluded that:

- (1) the firm diagnosis of rheumatic valvitis must depend in the discovery of a pansystolic or a diastolic murmur;
- (2) a soft, mid-systolic murmur in rheumatic fever is probably innocent, but only long-term observation can prove this;
- (3) the length of an organic systolic murmur in rheumatic fever is its principal distinguishing feature on the phonocardiogram.

*C. Bruce Perry.*

**Some Basic Unsolved Problems in the Prevention of Rheumatic Fever.** COBURN, A. F. (1957). *Ann. intern. Med.*, 47, 402. 4 figs, 19 refs.

**Problem of Fever in Patients with Valvular Heart Disease.**

ROSS, R. S., McKUSICK, V. A., and HARVEY, J. C. (1957). *J. Amer. med. Ass.*, **165**, 1. 18 refs.

**Indications of the Prevalence of Rheumatic Fever.**

(Indagini sulla diffusione delle malattie reumatiche.) ROBECCHI, A., CARTESEGNA, F., DANE, V., D'ORIA, R., and EINAUDI, G. (1957). *Reumatismo*, **9**, 271. 8 refs.

**Pulmonary Involvement in Rheumatic Fever.**

(Contributo alla conoscenza delle localizzazioni polmonari della malattia reumatica.) BARONCELLI, A., and CASA, G. (1957). *G. Clin. med.*, **38**, 1511. 2 figs, 11 refs.

**Frequency and Significance of Systolic Murmurs in the Pulmonary Area in the Course of Rheumatic Fever.**

(Frequenze e significato dei soffi sistolici sulla polmonare in corso di reumatismo articolare acuto.) DETTORI, M. (1957). *Riv. Clin. pediat.*, **60**, 308. 3 figs, 8 refs.

### Chronic Articular Rheumatism (Rheumatoid Arthritis)

**Rheumatoid Tenosynovitis.**

(La tenosinovite reumatoide.) LUCHERINI, T., and NATALE, P. (1957). *Reumatismo*, **9**, 141. 12 figs, 27 refs.

From the Rheumatological Institute, University of Rome, the authors describe two cases of rheumatoid tenosynovitis. Both presented with chronic tenosynovitis of insidious onset and some constitutional disturbance; arthritis was absent. Tender swellings of tendon sheaths were present over the backs of the wrists, popliteal fossae, and ankles. Very full biochemical investigations were carried out, the results of which are reported. Microscopical examination of biopsy specimens of synovial sheath showed lymphocytic infiltration, with some fibrosis and hypertrophy of villi.

Treatment with prednisone by mouth in a dosage of 40 mg. daily was effective in one case after 2 weeks; the other did not respond to this treatment, but did so to local injections of prednisone trimethylacetate. The literature is reviewed and the differential diagnosis of tenosynovitis discussed. The authors conclude that these two cases were rheumatoid in nature.

David Friedberg.

**L.E. Phenomenon in Rheumatoid Arthritis.**

FRIEDMAN, I. A., SICKLEY, J. F., POSKE, R. M., BLACK, A., BRONSKY, D., HARTZ, W. H., FELDHAKE, C., REEDER, P. S., and KATZ, E. M. (1957). *Ann. intern. Med.*, **46**, 1113. 10 figs, bibl.

The L.E. test was performed on 91 patients (46 males and 45 females) with classic rheumatoid arthritis, the Zimmer clot technique being used. In fourteen the results were strongly positive, in eight they were moderately positive, and in three weakly positive. Of these 25 patients, thirteen were males and twelve females. The authors point out that the incidence of positive results in this series is higher than in any previously reported study.

Distinguishing features in the patients giving a positive response included the absence of "pure" spondylitis and a high incidence of rheumatoid nodules, Felty's syndrome, and increased serum gamma globulin levels. Otherwise, there was no significant difference between patients giving a positive and those giving a negative reaction.

The authors conclude that the L.E. phenomenon is not specific for systemic lupus erythematosus, and that it may also occur in rheumatoid arthritis as a non-specific reaction.

E. G. Rees.

**Prednisone and Prednisolone Therapy in Rheumatoid Arthritis.**

**Clinical Evaluation, with Emphasis on Gastrointestinal Manifestations in 156 Patients observed for Periods of 4 to 14 Months.** STOLZER, B. L., BARR, J. H., EISENBEIS, C. H., WECHSLER, R. L., and MARGOLIS, H. M. (1957). *J. Amer. med. Ass.*, **165**, 13. 3 figs, 9 refs.

At the St. Margaret Memorial and Montefiori Hospitals, Pittsburgh, Pennsylvania, prednisone or prednisolone was given to 156 patients (60 males and 96 females), aged 9 to 78 years, suffering from rheumatoid arthritis. In 27 per cent. of the patients the duration of the disease was more than 15 years. In most of the cases the initial dosage ranged from 10 to 40 mg. daily, the maintenance dose being 10 mg. daily. [The authors do not distinguish between the two drugs as regards dosage or the results obtained.] The patients were observed for 4 to 14 months, the majority being under observation for more than 8 months. The results were assessed on the basis of activity of the disease, functional capacity, and, in the case of adult males, employability before and at some time during treatment. It was found that as regards activity of the disease 89 (59 per cent.) of the patients improved one grade (classification of Steinbrocker) and that in functional capacity 64 (41 per cent.) improved one grade. Of the thirty males who were unfit for work before treatment, nine went back to work during the course of treatment. Side-effects, such as moon face, nuchal hump, striae, and ecchymoses were noted in almost all of the patients. The number complaining of dyspepsia doubled during treatment, and x-ray examination of the gastro-intestinal tract in 43 who had severe dyspepsia showed peptic ulcer in seven. In addition, there were five cases of gastric haemorrhage or perforation, and in three patients hyperglycaemia with glycosuria developed, insulin being required by two of them. There were three deaths during treatment—one each from bile-duct cancer, perforation of the colon and general vasculitis, and gastric haemorrhage.

William Hughes.

**Macroglobulins in Rheumatoid Arthritis.**

**Preliminary Report.** [In English.] SVARTZ, N. (1957). *Acta med. scand.*, **158**, 163. 1 fig., 5 refs.

The remarkable circumstances has been brought to light that blood serum from patients suffering from rheumatoid arthritis may reveal the presence of a considerable amount of macroglobulins. This macroglobulin fraction has been found to contain the rheumatoid factor, i.e. that factor in rheumatoid arthritis which



is capable of inducing a certain type of haemagglutination reaction.—[Author's summary.]

**Peptic Ulceration occurring during Therapy for Rheumatoid Arthritis.** KERN, F., CLARK, G. M., and LUKENS, J. G. (1957). *Gastroenterology*, **33**, 25.

The conflicting reports in the literature on the incidence of peptic ulcer occurring during adrenal steroid and phenylbutazone therapy led the authors to study the clinical records of all patients with rheumatoid arthritis attending the arthritic clinic of the General Hospital, Colorado, over a recent 10-year period, with special reference to gastro-intestinal symptoms. The records of 169 patients (66 men and 103 women) were studied, dyspeptic symptoms being collated in relation to age, sex, duration of arthritis, and type of treatment. The diagnosis of peptic ulcer was accepted only if the presence of an ulcer had been confirmed radiologically, gastroscopically, or at operation. Peptic ulcer was present in twelve males and nine females, an incidence of 12.5 per cent., but six of the males had had an ulcer before the onset of rheumatoid arthritis, so that the over-all incidence of new ulcers was 9.2 per cent. (fifteen cases). The new ulcers were equally distributed between the duodenum and stomach (the site of one was unknown), in contrast to the old ulcers, five of which were duodenal.

In assessing the effect of treatment the authors assumed that in all cases variable amounts of aspirin were taken for pain during therapy with phenylbutazone and steroids. The dosages employed were: phenylbutazone 200 to 800 mg. a day, usually 400 mg. a day; prednisone or prednisolone 5 to 40 mg. daily; cortisone 25 to 100 mg. a day; and hydrocortisone 30 to 50 mg. daily. A new ulcer developed in seven patients taking phenylbutazone and in seven taking steroids (in one it developed before treatment started). These could not be related to the duration of therapy as this varied from 4 to 37 months for phenylbutazone and from 3 to 16 months for steroids. The dosage of the steroids, however, appeared to be of great importance, the critical level being in the region of 50 mg. cortisone and 15 mg. prednisone. Of the 116 patients receiving the lower dosage schedule a new ulcer developed in one only, whereas new ulcers were found in five out of 22 on the higher dosages. The duration of arthritis also appeared to increase the risk of developing an ulcer; this tendency, the authors state was not just a function of age. They conclude that there is a definite increase in the incidence of peptic ulcer in patients with rheumatoid arthritis, compared with the general population, and that this is related to treatment with steroids and phenylbutazone.

B. M. Ansell.

**Influence of Emotional and Endocrine Factors in the Clinical Picture of Rheumatoid Arthritis and Other Collagen Diseases.** (Influenza di fattori emotivi ed endocrini sul quadro clinico dell'artrite reumatoide e di altre collagenosi.) BONOMO, L. (1957). *Reumatismo*, **9**, 238. 2 figs, bibliography.

The first part of this report is based on the study of 150 cases of rheumatoid arthritis and forty cases of osteo-

arthritis seen at the West London Hospital. In 25 patients with rheumatoid arthritis (21 female and 4 male) the disease began or became much worse soon after pregnancy (five cases) or some other "modifying event" such as bereavement, accident, marriage, divorce, or difficulty in the family or at work. In a diagram the author demonstrates very clearly the initiation or aggravation of the disease for each of nineteen of these patients. By contrast, in the series of forty patients with osteoarthritis similar modifying events occurred in five, but in no case was the disease pattern altered. The difference between the two groups is statistically highly significant.

The second part reports a similar study in 52 patients with rheumatoid arthritis seen at the University Medical Clinic, Bari, in twelve of whom comparable "modifying events" resulted in aggravation of the disease. A similar phenomenon was also observed in five out of fifteen patients with polyarteritis nodosa and in four out of 34 with dermatomyositis. The literature on the subject is reviewed and the author discusses the possible modes of action of endocrine and psychological stimuli in causing aggravation of the collagen diseases.

H. David Friedberg.

**Effects of Animal Sera and Serum Albumin on Latex-Fixation Test for Rheumatoid Arthritis.** RHEINS, M. S., MCCOY, F. W., BUEHLER, E. V., and BURRELL, R. G. (1957). *Proc. Soc. exp. Biol. (N.Y.)*, **96**, 67, 12 refs.

The Rose-Waaler haemagglutination test is now widely employed in the serological study of rheumatoid arthritis. A modification of the test has recently been introduced by Singer and Plotz (*Amer. J. Med.*, 1956, **21**, 888; *Abstr. Wld Med.*, 1957, **22**, 50) in which the sensitized sheep erythrocytes are replaced by latex particles, the reaction of which with the rheumatoid (macro-gamma-globulin) factor requires the presence of human gamma globulin. This gamma-globulin factor is referred to in the present paper as the "antigen" which reacts with the antibody represented by the rheumatoid factor.

The antigenic properties in this latex-fixation reaction of sera from different animal species have been examined by the authors at the Ohio State University, Columbus. The whole sera were found to be ineffective, but all could be made active either by the removal of albumin by the sodium sulphate technique of Thurston or more simply by dilution. Human, rabbit, pig, guinea-pig, cat, horse, ox, and sheep sera so treated were all effective "antigens", whereas chicken serum and one specimen of dog serum produced agglutination in the saline controls. The inhibiting effect of albumin is thought to be due to its action as a non-specific protective colloid, similar inhibition being produced by the addition of gelatin. It is shown, in confirmation of the original work, that a concentration of globulin of at least 25 µg. per ml. is necessary to obtain its full reactivity as an "antigen". By suitable dilution of the whole serum the concentration of albumin can be reduced below the level at which it exerts its protective effect while that of globulin remains sufficient for "antigenic" fixation to the latex particles.

Harry Coke.



**Psychological Aspects of Rheumatoid Arthritis.** CORMIER, B. M., and WITTKOWER, E. D. (1957). *Canad. med. Ass. J.*, **77**, 533. 16 refs.

The motor activity of eighteen patients with rheumatoid arthritis has been compared with the motor activity of their nearest siblings free of the illness. The comparison shows that the rheumatoid arthritis patients are overactive as children but inhibited later in life (before their illness), whereas their siblings who are free of the illness start life with normal or inhibited motor activity and seem to be able to use their motor apparatus successfully for instinctual discharge later on in life.

Motor overactivity early in life in the rheumatoid arthritis patients seems to serve as an outlet for aggressive drives in a socially acceptable or unacceptable form. After puberty, overactivity is progressively abandoned as an inadequate means of expression of instinctual drives as well as a psychological defence against them. Deprived of discharge of instinctual tension in movement and impulsive action, the rheumatoid arthritis patients take recourse to aggressive fantasies which give rise to feelings of guilt and anxiety. The intensification of these incompletely recognized, intolerable, aggressive fantasies (and the concomitant guilt and anxiety) by disturbing events in the patient's life history often precedes and probably precipitates the onset of rheumatoid arthritis.

The comparison of the Rorschach findings in thirteen rheumatoid arthritis patients with the findings in the thirteen nearest siblings free of the disease corroborated closely the clinical assessment. The severity of the illness seems to be proportionate to the severity of the impairment in the capacity to express aggression. The psychotherapeutic implications of these findings are discussed with clinical examples.—[Authors' summary.]

**Ocular Changes in Juvenile Rheumatoid Arthritis. Report of a Case.** (Alteraciones oculares en la artritis reumatoidea juvenil. Caso clínico.) CHARLÍN V., C. (1957). *Arch. chil. Oftal.*, **14**, 58. 2 figs, 3 refs.

Both Still's disease and chronic deforming infantile polyarthritis cause iridocyclitis, band-shaped corneal opacity, and cataract. A case of deforming infantile chronic polyarthritis in a girl aged seven is presented with bilateral band-shaped opacities of the cornea and a long-standing iridocyclitis at the stage of pupillary occlusion and seclusion with some degree of thin, deep corneal vascularization. Still's disease was ruled out on account of the time of onset, lack of lymph gland involvement or splenomegaly, and the clinical course.

A. Gormaz B.

**Ocular Manifestations in Infantile Rheumatoid Arthritis.** (Ancora sulle manifestazioni oculari dell'artrite reumatoide infantile.) VOLPI, U., and ANDREANI, D. (1956). *Ann. Ottal.*, **82**, 601. 10 refs.

The report of a child with band-shaped keratitis, torpid iridocyclitis, and cataract. Although the patient had had amoebiasis from the onset of the ocular signs, the authors rule this out as the cause. There was an increased sedimentation rate and high antistreptolysin titre and the authors believe that despite the absence of

other evident clinical signs of arthritis this case may be attributed to rheumatoid arthritis. M. H. T. Yuille.

**Oculo-Articular Syndrome in Children.** [In Czech.] SVĚRÁK, J., and ISELE, J. (1957). *Čsl. Oftal.*, **13**, 420. 4 figs, 38 refs.

Three cases of Still-Chauffard's syndrome are described, the clinical picture and pathogenesis of the ocular signs are discussed, and the early diagnosis and treatment of children with chronic rheumatism are stressed.

M. Klima.

**Prolonged Treatment of Rheumatoid Arthritis with Prednisone (Meticorten).** COHEN, A., TURNER, R. F., KANENSON, W. L., and GOLDMAN, J. (1957). *J. Amer. med. Ass.*, **165**, 225. 1 ref.

From the Philadelphia General Hospital and Jefferson Medical College comes this report of the results of prolonged prednisone therapy of rheumatoid arthritis. Of 132 patients (56 males and 76 females, aged 17 to 75 years), 92 had had rheumatoid arthritis for more than a year and had been treated with gold, steroids, or phenylbutazone; the disease was acute in only four patients in the series. The dosage of prednisone varied, but with experience it became usual to give 5 mg. every 6 hours day and night for a week, and thereafter to decrease the daily dose by 2.5 mg. each week so long as symptoms did not return. The final maintenance dose was 2.5 to 15 mg. daily.

Complete remission was obtained in 39 cases, major improvement in 89, and minor improvement in four; with a few exceptions improvement could be maintained. There was no instance of sodium retention, and two patients with heart failure fared well. A transient rise in blood pressure occurred in eight patients during the first week of treatment. In three patients with peptic ulcer and one in whom acute perforation of a duodenal ulcer was treated surgically prednisone therapy was maintained satisfactorily. Of five patients with diabetes mellitus three required additional insulin, but prednisone was effective in all. Moon face occurred in seventy patients and acne in one only.

The authors conclude that the effect of prednisone is superior to that of the older steroids, and emphasize the absence of electrolyte disturbances and of hypertension.

David Friedberg.

**Prednisone and Prednisolone in the Treatment of Rheumatoid Arthritis.** MONTGOMERY, D. A. D. (1957). *Ulster med. J.*, **26**, 51. 11 refs.

**Changes in the Electrophoretic Behaviour of Arthritic Synovial Fluid Components following Intra-articular Steroid Therapy.** PLATT, D., HOLLEY, H. L., and PIGMAN, W. (1957). *J. Lab. clin. Med.*, **49**, 762. 14 refs.

**Intravenous Administration of Nitrogen Mustard Alone and with Corticotropin for Rheumatoid Arthritis.** SCHERBEL, A. L. (1957). *Cleveland Clin. Quart.*, **24**, 71.

**L.E. Phenomenon in Rheumatoid Arthritis.** PARR, L. J. A., SHIPTON, E. A., BENJAMIN, P., and WHITE, P. H. H. (1957). *Med. J. Aust.*, **1**, 900. 2 figs, 13 refs.

**Involvement of the Heart in Rheumatoid Arthritis.** (Zur Herzbeteiligung beim chronischen Gelenkrheumatismus.) GROS, H. (1957). *Z. Rheumaforsch.*, **16**, 392. 4 figs, 23 refs.

**Rheumatoid Arthritis with Lung Lesions.** EDGE, J. R., and RICKARDS, A. G. (1957). *Thorax*, **12**, 352. 7 figs, 25 refs.

**Double Blind Study using Manganese against Placebo in Rheumatoid Arthritis.** BEPLER, C. R., and ROGERS, F. B. (1957). *Amer. J. med. Sci.*, **234**, 459. 1 fig, 4 refs.

**Temporo-Mandibular Joint in Chronic Inflammatory Rheumatism and more particularly in Rheumatoid Arthritis.** (L'articulation temporo-maxillaire dans le rhumatisme inflammatoire chronique, et plus particulièrement dans la polyarthrite chronique évolutive.) ARLET, J., and CADENAT, H. (1957). *Rhumatologie*, No. 4, 185. 2 figs, 17 refs.

**Clinical and Radiological Studies of Respiratory Manifestations of Rheumatoid Arthritis.** (Rilievi clinico-radiologici di localizzazioni respiratorie nell'artrite reumatoide.) RIZZI, D., and CAVALLO, A. (1957). *G. Clin. med.*, **38**, 1521. 2 figs, 23 refs.

**Coincidence of Rheumatoid Arthritis and Schizophrenia.** PILKINGTON, T. L. (1956). *J. nerv. ment. Dis.*, **124**, 604. 4 refs.

**Objective Evaluation of Salicylates, Glucocorticoids, and Salicylate-Glucocorticoid Combinations in the Treatment of Rheumatoid Arthritis.** PAYNE, R. W., SHETLAR, M. R., HELLBAUM, A. A., and ISHMAEL, W. K. (1957). *J. Okla. St. med. Ass.*, **50**, 498, 528. 10 refs.

**Roentgen Demonstration of Soft Tissue Changes in Rheumatoid Arthritis.** [In English.] SOILA, P. (1957). *Acta rheum. scand.*, **3**, 328. 1 fig., 23 refs.

**Surgery of Rheumatoid Arthritis.** COZEN, L. (1958). *Rheumatism*, **14**, 2. 5 figs, 2 refs.

#### (Osteo-Arthritis)

**Osteo-Arthritis and Spondylosis of the Spine.** EPSTEIN, B. S., and EPSTEIN, J. A. (1957). *Rheumatism*, **13**, 82. 4 figs, 13 refs.

In this paper from the Long Island Jewish Hospital, New Hyde Park, New York, osteo-arthritis of the spine is discussed with special reference to pressure effects on the spinal cord and cauda equina. The radiological appearances and findings at operation are described. It is

pointed out that dorsal protrusion of osteoid tissue into the spinal canal is common and is often associated with thickening of the ligamenta flava and neural arches. Such protrusions may be clinically important when disk narrowing, spurring, and lipping are minimal; they may consist of unossified tissue which cannot be seen on a plain radiograph. Myelography is of value, but should not be carried out unless all conservative methods of treatment have failed.

The effects of cord compression by cervical spondylosis are discussed. In the lumbar region the authors have observed multiple ridges crossing the spinal canal and compressing the dura; symptoms may be bilateral and pain may be aggravated rather than relieved by rest in bed. Straight leg raising is sometimes normal. Laminectomy with removal of the ridges results in improvement.

K. C. Robinson.

**Osteophytosis of the Fovea: an Early Radiological Sign of Primary Osteo-Arthritis of the Hip.** (L'osteofitosi della fovea segno radiologico precoce dell'artrosi coxofemorale primaria.) DI VITTORIO, S., and MONATERI, P. C. (1957). *Reumatismo*, **9**, 305. 4 figs.

**Genetic Research into Predisposition to Painful Osteo-Arthritis and Its Relation to Primary Rheumatic Diseases.** (Ricerche genetiche sulla predisposizione all'artrosi "dolorosa" e sui suoi rapporti con i reumatismi primari.) SERNERI, G. G. N., and BARTOLI, V. (1957). *Acta Genet. med. (Roma)*, **6**, 503. 5 figs, 25 refs.

**Osteo-Arthritis with Emphasis on the Treatment of the Knee Joint.** BURGESS, T. W. (1957). *Med. J. Aust.*, **2**, 816. 4 refs.

**Medical Treatment of Osteo-Arthritis of the Hip.** (Traitement non sanglant de la coxarthrose.) COSTE, F. (1957). *Reumatismo*, **9**, 313.

#### (Spondylitis)

**Psoriatic Ankylosing Spondylitis.** (Á propos de la spondylarthrite psoriasique.) GRABER-DUVERNAY, J. (1957). *Rev. Rhum.*, **24**, 288. 6 figs, 24 refs.

The author presents from Aix-les-Bains a study of 23 cases (all in males) of ankylosing spondylitis associated with psoriasis. Of three of these cases described in detail, in two the spondylitis preceded the psoriasis by 28 and 25 years respectively and in the third the psoriasis appeared 28 years before the spondylitis. The author emphasizes, however, that these cases are not typical of the series. In fourteen the psoriasis appeared first, in only four did it follow the onset of spondylitis, and in the remaining five the onset of the two conditions was more or less simultaneous. It was reported by five patients that exacerbations of both conditions occurred simultaneously, six had found that they alternated, and the other twelve had noted no relationship. The age at onset of the spondylitis varied from 22 to 53 years; it was noteworthy that in three cases the age of onset was

over 50 years. In thirteen cases cervical symptoms developed, although these never appeared first. Peripheral joint affection was common, occurring in nineteen of the 23 cases, in nine of which a peripheral joint was the site of onset. The joints most frequently affected were those of the shoulder, knees and hands.

Heredity appeared to play an important part. A positive family history of psoriasis was obtained in six cases, of spondylitis in three, and of both conditions in one. The author points out that these cases differ sufficiently from the clinical picture of ankylosing spondylitis without psoriasis as to suggest that "psoriatic ankylosing spondylitis" may be a separate clinical entity.

B. E. W. Mace.

**Infantile Rheumatoid Spondylitis.** LUCCHESI, M., and LUCCHESI, O. (1957). *Rheumatism*, 13, 88. 2 figs, 10 refs.

The authors, writing from São Paulo, Brazil, discuss the findings in 31 children (19 female and 12 male) in whom rheumatoid spondylitis was diagnosed. The age at onset ranged from 9 months to 10 years, and the duration of symptoms from 7 days to 8 years. The predominant symptom was pain, which was usually transient but showed a marked tendency to recur, and affected mainly the lower limbs; it was not accompanied by joint swelling or stiffness. The majority of the patients did not show any involvement of the spine. There were no general signs, and fever was not observed. The blood count and the erythrocyte sedimentation rate were mainly normal. In two patients there was ankylosis in the cervical spine [but no other significant radiological abnormalities are reported]. In all cases x-ray therapy (288 to 720 r.) was given to the whole spine, with relief of symptoms, but the course of treatment had to be repeated once or twice in some instances.

K. C. Robinson.

**Some Aspects of the Histopathology and Pathogenesis of Ankylosing Spondylitis (Anatomical and Radiological Study of Two Cases, one being in the Active Stage).** (Considerazioni sul quadro istopatologico e sulla patogenesi della spondilite anchilosante.) BIRESSI, P. C., and MUSSA, L. (1957). *Reumatismo*, 9, 322. 23 figs, 58 refs.

#### (Miscellaneous)

**Ocular Manifestations of Rheumatism.** (Les manifestations oculaires du rhumatisme.) OFFRET, G., and MASSIN, M. (1957). Suppl. to *Bull. Soc. Ophthal. Fr.*, No. 6, pp. 82. 6 figs, bibl.

After a short description of rheumatism as a general disease, the authors study the clinical and ocular manifestations of each type of rheumatism.

Chronic septic polyarthritis is rheumatism of an inflammatory nature. This affects the small joints of the fingers and causes ankylosis, fever, and polynucleosis. The gamma-globulins increase with each attack. Scleroderma with subcutaneous Meynet's nodules is associated with the condition. The ocular manifestations of chronic septic polyarthritis are numerous. Sjögren's syndrome

with kerato-conjunctivitis sicca is often found (11 of 17 cases). Perforating scleromalacia is very rare but is of rheumatismal origin and has been seen in this type of rheumatism. Nodular scleritis, scleritis, episcleritis, and uveitis may all be found with chronic polyarthritis.

Spondylarthritis ankylopoietica is also of an inflammatory nature but involves the large joints and especially the spine and the hips, with formation of spurs, and overgrowths of the disks of the vertebrae. Uveitis or slight and torpid iritis are seen in 10 per cent. of the cases.

The oculo-urethro-synovial syndrome of Fiessinger-Leroy-Reiter is a manifestation of rheumatism. The clinical aspects and possible viral origin of this syndrome are discussed.

Acute articular rheumatism or Bouillaud's disease is frequently associated with band-shaped keratitis, iridocyclitis, or cataract.

Chronic cervico-arthritis may be complicated by Fuchs's sympathetic iritis, optic neuritis, or Adie's syndrome.

The report ends with a study of para-rheumatismal affections. Gout with gouty iritis, aphthosis with recurrent uveitis, or Behçet's disease, and collagen disease.

The authors reach the conclusion that many clinical ocular conditions are caused by rheumatism.

J. Rougier.

#### Diagnostic and Therapeutic Difficulties in Reiter's Disease.

**Five Personal Cases.** [In Polish.] KOTLEWSKI, M. (1957). *Polski Tyg. Lek.*, 12, 246.

On the basis of the five cases and the data from the literature the diagnostic difficulties even in the classical course of Reiter's syndrome are pointed out.

Treatment so far has not given lasting benefit. Antibiotics, such as aureomycin, terramycin or chloramphenicol, mostly help only individual symptoms of the syndrome. The best results were obtained with ACTH and cortisone (and intra-articular hydrocortisone) together with antibiotics. In cases combined with Bechterew's disease x-irradiation is necessary.

W. H. Melanowski.

**Regional Variations in the Innervation of the Deep Fasciae and Aponeuroses.** STILWELL, D. L. (1957). *Anat. Rec.*, 127, 635. 1 fig., 22 refs.

The innervation of the deep fasciae and aponeuroses has been studied at Stanford University, California, by gross dissection in eight human cadavers, and by intravital staining with methylene blue in seventeen monkeys and four rabbits. The fasciae are innervated by both deep and cutaneous nerves which may pass for some distance along the aponeuroses and tendons before ending in free arborizations of small-diameter fibres and encapsulate nerve endings. In most regions the endings are sparsely distributed compared with those in skin and periosteum, but in the hand and in the iliotibial tract nerve endings are particularly frequent. The functional implications of this type of innervation are fully discussed in the light of classic observations upon the sensory supply of deeper structures. Peter Ring.



**Non-rheumatoid Connective Tissue Disorders.** TALBOTT, J. H. (1957). *A.M.A. Arch. intern. Med.*, **100**, 535. 16 refs.

**Psychogenic Rheumatism.** (Psyko-rheumatism.) EDSTRÖM, G. (1957). *Nord. Med.*, **58**, 1957. 5 refs.

**Reiter's Syndrome in Females.** [In English.] REFVEM, O. *Acta rheum. scand.*, **3**, 282. 14 refs.

#### Disk Syndrome.

**Prednisolone by the Sacral Epidural Route in Sciatica.** (Il prednisolone per via epidurale sacrale nelle lombosciatalgie.) CAPPIO, M., and FRAGASSO, V. (1957). *Reumatismo*, **9**, 295. 7 refs.

#### Gout

**Overproduction of Uric Acid as the Cause of Hyperuricaemia in Primary Gout.** WYNGAARDEN, J. B. (1957). *J. clin. Invest.*, **36**, 1508. 2 figs, 31 refs.

In order to study the rate of generation of uric acid in gout radioactive glycine (glycine-1-<sup>14</sup>C) was fed to six patients with acute gouty arthritis, one with asymptomatic hyperuricaemia, and three control subjects, in doses of 2.5 to 25  $\mu$ C, and the degree of its incorporation in excreted uric acid measured, the concentration of <sup>14</sup>C in the daily output of uric acid being determined for 6 to 9 days after the dose was given.

When the cumulative incorporation of <sup>14</sup>C over several days was studied, the gouty subjects and hyperuricaemic subject were found to differ from the controls in the greater efficiency with which they used the tracer doses of glycine-1-<sup>14</sup>C in the synthesis of uric acid. There was no overlap between the two groups, the degree of incorporation of <sup>14</sup>C into uric acid in the former being 2 to 5 times higher than in the latter (0.29 to 0.66 per cent. of the dose of <sup>14</sup>C compared with 0.1 to 0.2 per cent. in 6 to 8 days). When a carrier dose of unlabelled glycine was given together with the tracer dose of glycine-1-<sup>14</sup>C to two gouty patients, the incorporation of <sup>14</sup>C into uric acid was greatly reduced. The results suggest that overproduction of uric acid from glycine and other small molecules is the fundamental defect in primary gout, and that nucleic acids are not involved in this process.

C. L. Cope.

**New Data on the Mode of Action of Colchicine in the Light of Recent Research.** (Données nouvelles sur le mode d'action de la colchicine à la lumière de recherches récentes.) MUGLER, A., and DU CHATELIER, G. G. (1957). *Rev. Rhum.*, **24**, 518. 4 figs, 42 refs.

**Saturnine Gout. A Secondary Type of Gout.** LUDWIG, G. D. (1957). *A.M.A. Arch. intern. Med.*, **100**, 802. Bibl.

#### Pararheumatic (Collagen) Diseases

**Serum Factor in Lupus Erythematosus with Affinity for Tissue Nuclei.** HOLBOROW, E. J., WEIR, D. M., and JOHNSON, G. D. (1957). *Brit. med. J.*, **2**, 732. 6 figs, 7 refs.

An investigation carried out at the Canadian Red Cross Memorial Hospital, Taplow, Bucks., showed that serum giving a positive reaction to the L.E. test contained a globulin factor with affinity for tissue nuclei. Tissue and cell preparations were treated with anti-human-globulin serum conjugated with fluorescein isocyanate and examined microscopically under ultraviolet light. Sections of tissue when pre-treated with L.E.-positive serum showed apple-green fluorescence where the conjugate had reacted with fixed globulin derived from the L.E.-positive serum. The L.E.-positive serum was obtained from two patients with systemic lupus erythematosus and one with severe and ultimately fatal rheumatoid arthritis. Fluorescence of cell nuclei following the treatment was observed in sections of skin, myocardium, kidney, thyroid, and spleen. This was not seen, however, when normal sera was used for treating the sections. Similar results were obtained when smears of leucocytes were examined in the same way.

E. G. Rees.

**Affinity between the Lupus Erythematosus Serum Factor and Cell Nuclei and Nucleoprotein.** HOLMAN, H. R., and KUNKEL, H. G. (1957). *Science*, **126**, 162. 1 fig., 3 refs.

This report from the Rockefeller Institute for Medical Research, New York, presents evidence suggesting that the lupus erythematosus (L.E.) factor combines directly with cell nuclei and nucleoprotein. In these studies nuclei from calf thymocytes, rabbit polymorphonuclear leucocytes, and human monocytes were incubated for 30 minutes at 18° to 38° C. with samples of highly positive L.E. serum. After removal of the nuclei by centrifugation the sera were found to have lost the ability to induce L.E.-cell formation. That the factor adheres to the nuclei was shown by the fact that nuclei which had been removed from L.E. serum and washed in saline until free of protein were still capable, when incubated with fresh human leucocytes, of being phagocytosed to form typical L.E. cells. Nuclei exposed to normal serum were not phagocytosed. The L.E. factor absorbed into the nuclei could be partially eluted by incubating the nuclei in isotonic saline at 45° to 65° C.

Similar experiments were conducted with isolated nuclear nucleoprotein. Removal of deoxyribonucleic acid (DNA) with deoxyribonuclease destroyed these properties, but treatment with ribonuclease did not impair absorptive capacity. Pre-treatment of nuclei with protamine or with "atabrine" (mepacrine) interfered with their ability to absorb the L.E. factor. Studies by the fluorescent antibody technique showed localization of  $\gamma$  globulin—presumably L.E. factor—on the affected nuclei in L.E. preparations. The possibility of the L.E. factor being an auto-antibody to nucleoprotein or deoxyribonucleic acid is considered.

E. G. Rees.

#### Comparative Evaluation of the Sensitivity of the L.E. Cell Test performed simultaneously by Different Methods.

DUBOIS, E. L., and FREEMAN, V. (1957). *Blood*, **12**, 657. 7 figs, 19 refs.

For a comparative investigation of the merits of the various methods of performing the L.E. test the authors, at the University of Southern California and the County



General Hospital, Los Angeles, carried out simultaneously a battery of these tests on peripheral blood from one venepuncture: at the same time they studied the effects of anticoagulants, coagulation, and leucocyte trauma on the L.E. phenomenon. A modification of the rotary glass bead technique of Zinkham and Conley was found to be the most sensitive, the sieved clot method and the ring technique of Snapper and Nathan being somewhat less sensitive. Heparin in concentrations greater than the minimum necessary to prevent coagulation exerted an inhibitory effect on the L.E. phenomenon.

E. G. Rees.

**Cytochemical Study of the L.E. Bodies of Systemic Lupus Erythematosus. I. Nucleic Acids.** GODMAN, G. C., and DEITCH, A. D. (1957). *J. exp. Med.*, **106**, 575. 9 figs, bibl.

The authors describe cytochemical investigations carried out at Columbia University and the Presbyterian Hospital, New York, on L.E. bodies and cells and also on blood lymphocytes for comparison. In methanol-fixed smears stained with Wright's stain suitable cells were mapped to permit re-location during subsequent manipulations. The experimental methods are fully described. The ability of the basic dye methyl green to combine with deoxyribonucleic acid (DNA) can be inhibited in varying degree by blocking the stainable groups of the nucleic acid with protein, and also by depolymerization. The effect of acetylation (which covers basic groups of proteins) on methyl-green binding by DNA in L.E. bodies has shown that over one-half of their stainable groups are masked by protein, whereas in normal lymphocyte nuclei less than one-tenth of the groups are pre-empted in this way. The intensity of staining by the Feulgen reaction is independent of changes in configuration of the DNA molecule or its relation to protein.

In untreated smears the ratio of methyl-green staining to the Feulgen reaction in L.E. bodies was found to be greatly decreased as compared with the lymphocyte nuclei, whereas after acetylation this ratio approached unity. This finding is interpreted as meaning that there is no decrease in methyl-green staining of L.E. bodies which cannot be accounted for by protein, and thus there is no need to invoke depolymerization of DNA to explain this phenomenon. These remarks apply particularly to free L.E. bodies, and not to L.E. bodies that have been phagocytosed for a long period. Incubation with ribonuclease was shown to cause a reduction in methyl-green staining which was much greater than that to be expected from loss of stainable DNA alone. The significance of this finding is not yet apparent. E. G. Rees.

**II. Proteins.** GODMAN, G. C., and DEITCH, A. D. (1957). *J. exp. Med.*, **106**, 593. 16 figs, 41 refs.

In this further communication from Columbia University, the authors describe investigations designed to determine the nature of the protein in the L.E. body. The total protein in free L.E. bodies and in lymphocyte nuclei was estimated by noting the capacity to bind the anionic dye naphthol yellow S (flavionic acid) and the results compared with the intensity of staining by the Feulgen reaction. When lymphocytes were incubated with serum from cases of lupus erythematosus it was shown that during their conversion to L.E. bodies there was a more than twofold increase in protein with no loss of deoxyribonucleic acid (DNA), as revealed by the Feulgen reaction. This was so despite the fact that there is early loss of histones in L.E. transformation, as revealed by the alkaline-fast methyl-green technique.

It is therefore postulated that the L.E. transformation entails an influx of protein normally foreign to the nucleus, displacement of histones from combination with DNA, and the association of DNA with the new protein

E. G. Rees.

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## PREVALENCE OF RHEUMATOID ARTHRITIS IN URBAN AND RURAL POPULATIONS IN SOUTH WALES

BY

W. E. MIALL

*From the Medical Research Council's Pneumoconiosis Research Unit, Llandough Hospital, Cardiff,*

AND

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The wide range of estimates of the prevalence of rheumatoid arthritis which is evident from a study of surveys undertaken in Great Britain and other countries (Cobb and Lawrence, 1957; Cobb, Warren, Merchant, and Thompson, 1957) is open to two interpretations: either large regional differences do exist or the diagnostic criteria adopted in these surveys are insufficiently standardized for valid comparison of the findings. Though the former explanation may be the correct one, the latter is certainly true also, and differences reported at present can be attributed as much to diagnostic criteria and population selection as to true epidemiological variations in prevalence.

In a first attempt to remedy this deficiency, the Manchester University Rheumatism Centre and the Medical Research Council's Pneumoconiosis Research Unit have pooled their resources and carried out a number of population studies (Miall, Caplan, Cochrane, Kilpatrick, and Oldham, 1953; Kellgren and Lawrence, 1956).

In this paper we summarize the results of two of these co-operative investigations. More detailed accounts of some of this work have already been published (Ball, 1955; Miall, 1955); reports of other joint studies will follow. The purpose of this paper is to describe the material from these two studies as a whole, and to discuss the validity of the diagnostic criteria used and methods of population sampling for this type of work.

### Methods

(1) **Choice of Population.**—The prevalence of a number of common diseases has been measured by the M.R.C. Pneumoconiosis Research Unit in two geographically defined areas in South Wales (Cochrane, Cox, and

Jarman, 1955; Miall and Oldham, 1955; Thomas, Cotes, and Higgins, 1956; Cochrane, Miall, and Clarke, 1956); the Rhondda Fach is a typical densely populated mining valley with a population of about 20,000 people aged 15 years or more. The Vale of Glamorgan is an agricultural area surrounding the small market town of Cowbridge. The population here comprised about 4,600 people aged 15 years or more. Each population was defined by private census shortly before the surveys. The two areas were chosen to provide neighbouring urban and rural populations in which the epidemiology of common diseases could be studied and compared. Their geographical centres were separated by about 15 miles.

(2) **Techniques.**—These surveys were undertaken in 1953 and 1955. At the time of the census in each area, an adult member of each household was asked to give the names of any individuals in the home who were thought to have arthritis or rheumatism. Subsequently 90 per cent. of the Rhondda Fach population and 95 per cent. of that in the Vale, attended a centre for chest radiography. As each subject attended, he or she was questioned about painful swelling of the small joints of the hands and feet. From these sources, and from rheumatism clinics, general practitioners, and gossip with cases of known rheumatoid arthritis, visiting lists were compiled, and all these people were interviewed by a physician in their homes. On the basis of the history and any physical signs present in accessible joints, those who were thought to be possible cases of rheumatoid arthritis, or to have had a past poly-arthritis of the rheumatoid type, were asked to attend a centre for further investigation.

These two surveys differed in only one important way. The screening was deliberately made at a lower threshold during the Vale of Glamorgan survey. This resulted in relatively more subjects being included with only vague and indefinite symptoms, and no residual physical signs, of arthritis. In both surveys subjects showing only the physical signs of degenerative arthritis were included if

their symptoms suggested that there had also been an episode of rheumatoid arthritis.

Diagnostic Criteria

The standardization of diagnostic criteria has been met by including radiographical and serological data. Radiographs were taken of the hands and feet with a control bone to facilitate the assessment of osteoporosis. All films were read by a single observer (J.H.K.). The sheep cell agglutination tests for rheumatoid arthritis were all performed in one laboratory by the method of Ball (1950). Agglutination at a titre of at least 1 in 32 after 18 hrs' incubation was accepted as a positive result. In each case precautions were taken to avoid any secular changes in standards. Steps were also taken to ensure that the opinion of the observer grading the films corresponded with the mean opinions of three other clinicians and two radiologists, all of whom had a special interest and experience in rheumatic diseases (Kellgren, 1956). Further studies concerning grading of the radiological changes of both rheumatoid and osteo-arthritis in hand films, together with illustrations of agreed grades of change, are being published elsewhere (Kellgren and Lawrence, 1957a, b).

No defined standards were used for the clinical diagnosis of rheumatoid arthritis—this was largely left to clinical judgment, which was based on a history, with or without residual physical signs, of polyarthritis with characteristic symmetrical affection of certain peripheral limb joints with soft tissue swelling rather than bony enlargement, often accompanied by morning stiffness, constitutional disturbances, and occasionally by subcutaneous nodules.

In surveys of this kind, a standard of reproducible diagnosis is essential. Unfortunately the diagnostic difficulty in rheumatism is considerable, except in its more severe forms. In these screened populations, subjects have not been investigated unless a characteristic history was obtained, and they have been rejected if this history was not confirmed by radiological or serological evidence of the disease. Though it is not claimed that all rheumatoid arthritis satisfies these criteria, probably few false positive results are obtained, and for comparative purposes a reproducible diagnosis at a high threshold is more useful than an unreproducible one at a lower threshold.

Response Rates

The population in the Rhondda Fach and the Vale of Glamorgan is shown in Table I, together with the number of people who passed the initial screening for polyarthritis. The marked differences in the overall percentages of the populations who passed this preliminary screening reflect only the different criteria used at this stage, but we believe that the final criteria which had to be satisfied for the arthritis to be accepted as rheumatoid were sufficiently strict to overcome these differences in screening procedure.

Table II (opposite) shows the rates in the investigation of suspected cases in the two surveys. Of 474 suspected cases, 449 (95 per cent.) were investigated either by x ray or serologically, and 391 by both methods (82 per cent.). Among those not investigated were eight severe and bedridden cases of typical rheumatoid arthritis who have been presumed positive; those who refused or were unable to be investigated have been included as

TABLE I  
PREVALENCE OF SUSPECTED RHEUMATOID ARTHRITIS BY AGE AND SEX, RHONDDA FACH (1953) AND VALE OF GLAMORGAN (1955)

Survey	Age (yrs)	Females			Males		
		Population	Suspected Cases		Population	Suspected Cases	
		No.	No.	Per cent.	No.	No.	Per cent.
Rhondda Fach	15-	1,857	—	—	1,640	—	—
	25-	1,953	10	0.5	1,957	12	0.6
	35-	1,856	15	0.8	1,725	16	0.9
	45-	1,719	39	2.3	1,612	30	1.9
	55-	1,477	68	4.6	1,301	21	1.6
	65+	1,430	51	3.6	1,195	20	1.7
	Total	10,292	183	1.8	9,430	99	1.1
Vale of Glamorgan	15-	369	3	0.8	365	—	—
	25-	464	10	2.2	464	2	0.4
	35-	403	17	4.2	426	8	1.9
	45-	439	41	9.3	410	12	2.9
	55-	339	38	11.2	311	22	7.1
	65+	328	22	6.7	303	17	5.6
	Total	2,342	131	5.6	2,279	61	2.7

TABLE II

RESPONSE RATES IN THE INVESTIGATION OF SUSPECTED CASES, RHONDDA FACH (1953) AND VALE OF GLAMORGAN (1955)

Survey	Sex	Age (yrs)	Suspected Cases			Investigated			Not Investigated		
			Total	Investigated	Not Investigated	X ray and S.C.A.T.	X ray Only	S.C.A.T. Only	Bedridden with R.A.	Assumed Positive	Assumed Negative
Rhondda Fach	Females	15-25-	10	10		9	1				
		25-35-	15	14	1	8	6				1
		35-45-	39	37	2	33	4			1	1
		45-55-	68	66	2	54	10	2	1	1	
		55-65+	51	44	7	27	14	3	3	1	3
		Total Per cent.	183 (100)	171 (93)	12 (7)	131 (72)	35 (19)	5 (3)	4 (2)	3 (2)	5 (3)
	Males	15-25-	12	12		11	1				
		25-35-	16	16		13	3				
		35-45-	30	28	2	26	1	1		1	1
		45-55-	21	21		17	2	2			
		55-65+	20	20		18	1	1			
		Total Per cent.	99 (100)	97 (98)	2 (2)	85 (86)	8 (8)	4 (4)	0	1 (1)	1 (1)
Vale of Glamorgan	Females	15-25-	3	2	1	1	1				1
		25-35-	10	10		10					
		35-45-	17	17		17					
		45-55-	41	39	2	37	2				2
		55-65+	38	35	3	34	1	1	1	2	2
		65+	22	18	4	17					
		Total Per cent.	131 (100)	121 (92)	10 (8)	116 (89)	4 (3)	1 (1)	3 (2)	2 (2)	5 (4)
	Males	15-25-	2	2		2					
		25-35-	8	8		8					
		35-45-	12	12		12					
		45-55-	22	22		22					
		55-65+	17	16	1	15	1		1		
		Total Per cent.	61 (100)	60 (98)	1 (2)	59 (97)	1 (2)	0	1 (2)	0	0

positive only if the home visit notes showed clear evidence of undoubted rheumatoid disease.

### Results

The prevalence of confirmed rheumatoid arthritis by age is shown in Table III (overleaf) for the two surveys.

"Confirmed" rheumatoid arthritis, as here defined, refers to those cases of polyarthritis in which the diagnosis was confirmed as rheumatoid either by radiological changes in the films of the hands or feet, or by the sheep cell agglutination test, or by both.\*

This Table shows that the overall prevalence according to these strict criteria is almost equal in females and males in both the Rhondda Fach and the Vale of Glamorgan. Ball (1955) has shown

that, after allowing for duration and severity of arthritis, agglutination occurs at higher titres in the sheep cell test when rheumatoid arthritis is associated with the progressive massive fibrosis of coalworkers' pneumoconiosis. In populations containing large numbers of miners and ex-miners, therefore, it could be argued that these criteria could artificially swell the number of confirmed rheumatoid arthritis amongst the men. The number of subjects with a characteristic history confirmed only by a positive sheep cell test is shown in the middle columns of this Table, and it is evident that the numbers of such cases are roughly equal in the two sexes. The third column, showing the difference between the first two, gives the prevalence of symptomatic cases with radiological confirmation in the hands and/or feet together with the small number of obvious and mostly bedridden cases.

These prevalence data for the two areas are set out in Fig. 1 (overleaf), which shows two striking

\* The fourteen advanced cases (eight of whom were bed-ridden), who were not investigated, are included as "confirmed" cases.



TABLE III

PREVALENCE OF CONFIRMED RHEUMATOID ARTHRITIS BY AGE AND SEX, RHONDDA FACH (1953) AND VALE OF GLAMORGAN (1955)

Survey	Sex	Age (yrs)	Population	Confirmed by					
				Positive X ray and/or Positive S.C.A.T.		Positive S.C.A.T. Only		Positive X ray or Obvious Signs	
				No.	Per cent.	No.	Per cent.	No.	Per cent.
Rhondda Fach	Females	15-	1,857						
		25-	1,953	3	0.2	2	0.1	1	0.1
		35-	1,856	1	0.1			1	0.1
		45-	1,719	17	1.0	7	0.4	10	0.6
		55-	1,477	28	1.9	5	0.3	23	1.6
		65+	1,430	17	1.2	2	0.1	15	1.1
	Total		10,292	66	0.6	16	0.2	50	0.5
	Males	15-	1,640						
		25-	1,957	7	0.4	2	0.1	5	0.3
		35-	1,725	10	0.6	4	0.2	6	0.4
		45-	1,612	20	1.2	4	0.3	16	1.0
		55-	1,301	15	1.2	5	0.4	10	0.8
		65+	1,195	11	0.9	2	0.2	9	0.8
	Total		9,430	63	0.7	17	0.2	46	0.5
Vale of Glamorgan	Females	15-	369						
		25-	464						
		35-	403	1	0.3			1	0.3
		45-	439	2	0.5			2	0.5
		55-	339	9	2.7			9	2.7
		65+	328	13	4.0			13	4.0
	Total		2,342	25	1.1	0		25	1.1
	Males	15-	365						
		25-	464						
		35-	426	2	0.5			2	0.5
		45-	410	3	0.7			3	0.7
		55-	311	5	1.6	1	0.3	4	1.3
		65+	303	12	4.0	1	0.3	11	3.6
	Total		2,279	22	1.0	2	0.1	20	0.9

features: first, the very different shapes of the curves relating prevalence and age in the two areas which is apparent in both sexes; secondly, the similarity in the prevalence curves for males and females in the two surveys. In the Rhondda Fach, where the prevalence is higher in the younger age groups, it reaches a maximum between the ages of 45 and 64 years, and then becomes less in the elderly, whereas in the Vale of Glamorgan the prevalence goes on rising in the older age groups in both sexes. The resultant differences in prevalence in those over 65 years of age are significant at the 2 per cent. level. These features are discussed later.

#### Discussion

**Survey Technique.**—We are fully aware that surveys of symptomatic disease are far from ideal; in this as in most chronic diseases there is a significant group of affected people who are either asymptomatic or who have such vague or bizarre symptoms that they are not easily revealed by simple screening questions. We believed from the outset that the most valuable information would result

from identifying all cases of classical rheumatoid arthritis in the populations studied, and that the type of case in which there was involvement only of spinal or larger limb joints could be ignored without introducing biases.

The results of the investigation by Kellgren and Lawrence (1956) of a random sample of the urban population of Leigh, Lancashire, suggested that a clinical opinion about the presence or absence of rheumatoid arthritis might have little significance except for severe classical cases; one of the disturbing features was the number of subjects with positive agglutination tests, or positive radiographs, in whom no evidence of rheumatoid arthritis was recorded at the clinical examination.

We have therefore to be clear about what we are investigating. If rheumatoid arthritis is defined as a polyarthritis of the peripheral limb joints the type of screening test we used in these two surveys, which is based on a history of painful swellings of the small joints of the hands and feet, may be a good one; but if rheumatoid arthritis is one manifestation of a form of connective tissue disease associated with

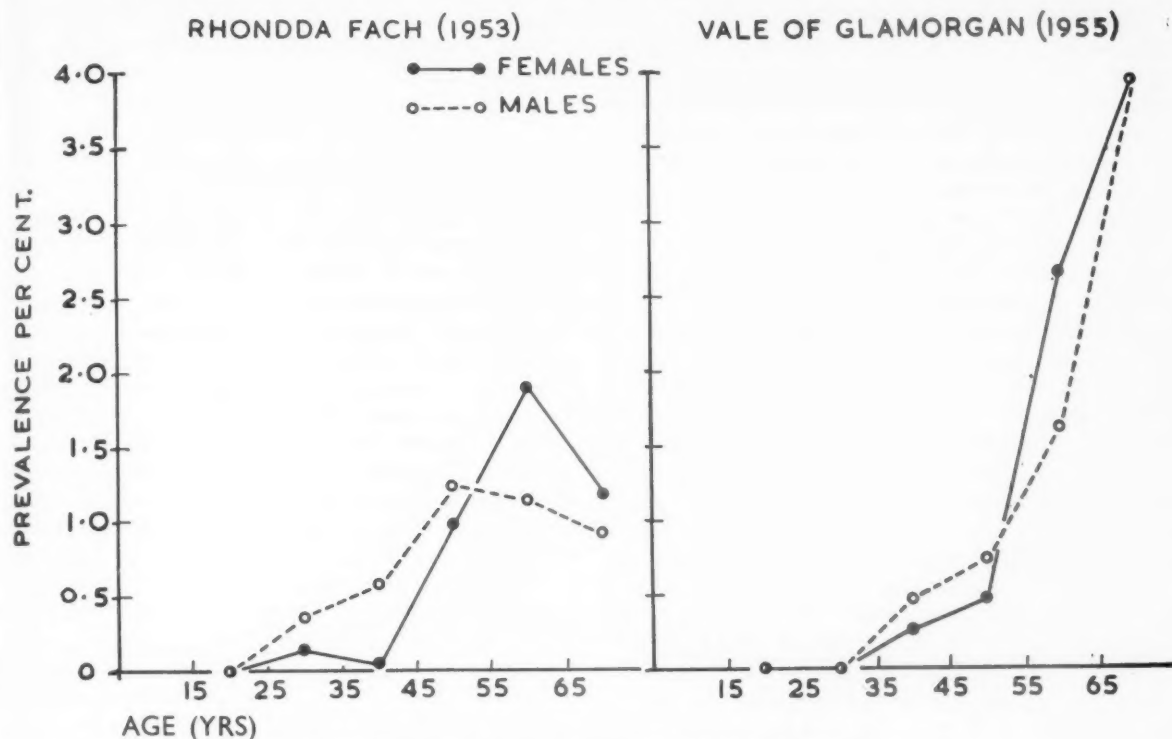


Fig. 1.—Prevalence of confirmed rheumatoid arthritis in the two surveys.

a positive agglutination test, then a screening technique designed for arthritis of the hands and feet may be too exclusive.

There is another weakness of screening in this way: we have no knowledge that different populations respond identically to the questions. The alternative approach is to investigate fully random samples of populations, but this would be extremely laborious if adequate numbers from all age groups were studied. It appears likely that a combination of both these methods of study will be found to produce the most useful information, and later we hope to report the results of investigations of random samples of these and other geographically defined populations, which should supplement the present findings.

**Differences in Prevalence between the Rhondda Fach and the Vale of Glamorgan.**—Before attributing the differences we have found to epidemiological factors, we must be sure that they are not artefacts either due to the screening or resulting from differential migration in the two areas. The initial screening was identical in the two populations and covered all age groups equally well in both areas. The clinical

screening was deliberately altered between the two surveys, but we do not believe that this has materially influenced the threshold for those satisfying such strict criteria. The lower threshold for symptoms used in the Vale produced the expected difference between the number of suspected and confirmed cases in all age groups except those over 65, where the figures for confirmed and suspected cases became thirteen out of 22 for females and twelve out of seventeen for males, compared with the Rhondda figures of seventeen out of 51 for females and eleven out of twenty for males. The larger change for the females is, we believe, due to the inclusion of relatively more cases of generalized osteo-arthritis in the earlier survey. Nothing is as yet known about the prevalence of asymptomatic serological and radiological findings in those over 65, and it is conceivable that this may increase abruptly in old age to a substantial proportion of the population, in which case prevalence rates of rheumatoid arthritis in those over 65 would be greatly affected by the proportion of individuals investigated. However, the differences in prevalence between the two areas are almost unchanged if the analysis is confined only to those with moderate and severe radiological changes.

In general it is the healthier section of the population that migrates (Hill, 1925). We should therefore expect high prevalence rates for diseases in the residual populations where migration has been great; it is likely that migration has been greater from the Rhondda than from the Vale, and thus migration would have biased the results in the opposite direction to those found.

None of the elderly rheumatoid arthritics in the Vale had come into the area since developing arthritis. We feel justified, therefore, in assuming that the differences are true epidemiological ones; a fall in prevalence among the elderly, as in the Rhondda data, must mean either that the combination of the case recovery rate and the case fatality rate is exceeding the attack rate amongst the elderly, or that the disease, the mean age of onset of which is in the fifth decade in our data, is becoming more common. On the other hand, a prevalence curve showing highest rates in the elderly, as in the Vale of Glamorgan, could be explained by an attack rate in the elderly which exceeds the combined cure rate and mortality rate, or by the disease becoming less common in the last few decades.

The prevalence of severely disabled cases is certainly higher in the Rhondda except above age 65; the mean age of onset in females was almost identical in the Rhondda and Vale (48 and 47 years respectively), but males were attacked on the average 10 years earlier in the Rhondda (43 to 53 years). In both sexes, for the same degree of radiological disease, the sheep cell tests were positive at higher titres in the Rhondda than in the Vale. Table IV shows the data for all subjects in whom there were both radiological and sheep cell test results available, except for miners with massive fibrosis, who have

been omitted from this Table because of the enhanced agglutination titres associated with this condition. The overall difference between the Rhondda Fach and Vale data in Table IV is statistically significant at the 2 per cent. level.

If, as our data suggest, rheumatoid arthritis is occurring earlier in the Rhondda Fach and in a more severe form and if prolonged rheumatoid arthritis is accompanied by a significant mortality from intercurrent disease as shown by Cobb, Anderson, and Bauer (1953), this could explain some of the difference between the areas. A preliminary comparison of the 4-year follow-up of the Rhondda Fach rheumatoid population with controls balanced for age and sex shows that the female rheumatoid arthritic patients have suffered a significant excess mortality over their controls; the males have shown no such significant difference, despite their high prevalence of massive fibrosis (Miall, 1955). Attack rate and mortality studies which will be obtained from the continued follow-up of these populations may explain the differences between rheumatoid arthritis in the two areas.

**Sex Differences in Prevalence.**—Perhaps the most surprising finding from these two surveys in South Wales is that the prevalence of rheumatoid arthritis satisfying these strict criteria was equal in the sexes, whereas clinical polyarthritis was found much more frequently in women. Similar results were found by Kellgren and Lawrence (1956) in their population sample of the inhabitants of Leigh. Clinical polyarthritis of a rheumatoid type was much more common in females, but the distribution of the grades of radiological changes was similar in the two sexes; this is also true of random samples of the

TABLE IV  
RELATIONSHIP BETWEEN RADIOLOGICAL RHEUMATOID ARTHRITIS AND SHEEP CELL AGGLUTINATION TITRE IN THE RHONDDA FACH AND THE VALE OF GLAMORGAN

Sex		Females						Males					
Radiological Grade of Rheumatoid Arthritis		2		3		4		2		3		4	
		Rhondda	Vale	Rhondda	Vale	Rhondda	Vale	Rhondda	Vale	Rhondda	Vale	Rhondda	Vale
Reciprocal of Titre	<4	3	4		1	1	1		6	1	3		
	4								1			1	
	8	2		3	1	1		2	4				
	16	1	1	1				1		1			
	32	1	1		1	1	1					1	
	64	2	1		2	2	3	1	1				
	128	2		2		1	2	1	2			1	
	256	2				2	1	2		2		1	1
	512			3		3				1		1	
	1,024					2				2		2	
	2,048									1		1	
	4,096					1							
Total	.. ..	13	7	9	5	14	8	10	14	8	3	8	1

same age group of the Vale of Glamorgan population, which we shall discuss fully elsewhere.

Furthermore, the agglutinating titres in the sheep cell test were distributed in a similar manner in both sexes in the Leigh sample. One explanation for this difference between the subjective and the objective findings would be a lower complaint threshold amongst women, since a clinical diagnosis of polyarthritis is largely determined by a complaint of pain, swelling and joint stiffness.

However, there are other possibilities. Table I shows the numbers of suspected rheumatoid arthritics in these surveys of clinical disease to have the expected preponderance of females.

Fig. 2 (1), overleaf, shows the prevalence of such cases for the Rhondda Fach by age and sex. At the level of screening used in that survey, the female preponderance is largely restricted to those aged 50 years or more. In these surveys a number of cases of multiple osteo-arthritis were investigated because their medical histories, including previous treatment, suggested an episode of rheumatoid arthritis.

Fig. 2 (2), overleaf, shows the effect on the prevalence of suspected rheumatoid arthritis of the removal of all those who eventually showed only evidence of multiple osteo-arthritis with no definite radiological or serological evidence of rheumatoid disease. The remaining cases, consisting of rheumatoid arthritics and subjects with a polyarthritis, the nature of which could not be confirmed radiologically or serologically, then showed a much reduced sex difference in prevalence.

In the Vale of Glamorgan survey, which allowed investigation of a greater number of extremely doubtful cases, the prevalence of suspected disease is naturally much higher (Fig. 2 (1)), and the sex difference is greater throughout, except in the oldest age group where degenerative arthritis and rheumatoid arthritis are most easily distinguished. Removing those who ultimately showed only evidence of osteo-arthritis diminishes the prevalence at ages 45, 55, and 65+ (Fig. 2 (2)) in women, but still leaves a marked sex difference in the younger age groups. As it disappears when only confirmed cases of rheumatoid arthritis are considered, this sex difference is again due to subjects with a polyarthritis which failed to satisfy objective criteria of either rheumatoid or osteo-arthritis. This sex difference in the younger age groups remains to be explained; it could be due to unconfirmed rheumatoid disease or to unconfirmed early multiple osteo-arthritis. We should, however, examine the evidence that this generalized osteo-arthritis is not osteo-arthritis secondary to rheumatoid arthritis. The former condition is found predominantly in middle-aged

women and often appears to have a rather acute spontaneous onset; affected joints tend to pass through two stages, an initial acute phase during which the joints may be warm, red, tender, and swollen, and after a period of several months this is followed by a chronic phase, characterized by bony outgrowths around the joint margins (Kellgren and Moore, 1952). It is not surprising therefore that, when this process involves those joints which are characteristically affected by rheumatoid arthritis, the differential diagnosis may be extremely difficult (Cobb, Merchant, and Rubin, 1957). This is particularly true perhaps under survey conditions, for the subjects are not necessarily seen when they have the kind of active disease which brings them to hospital. Further difficulty is introduced because rheumatoid arthritis and generalized osteo-arthritis are common diseases and may co-exist in the same individual.

An examination of the radiological data for the Leigh random sample shows no positive correlation between radiological rheumatoid and osteo-arthritic disease. There is in fact a low negative association between the two conditions; a person with rheumatoid arthritis appears less liable to osteo-arthritis than a normal subject, and conversely a person with osteo-arthritis appears less liable to rheumatoid disease than would be expected if the conditions were independent. We hope to discuss this when further sets of radiographs from random samples are available. If this type of multiple osteo-arthritis were frequently secondary to rheumatoid arthritis, we should expect to be able to detect radiological evidence of rheumatoid changes in the more severe cases. Furthermore, if it occurred secondary to an onset of rheumatoid arthritis in middle-aged females, one would expect, in these surveys, a marked excess of confirmed cases in females over males in middle-age. This was not found in the South Wales surveys. Ball (1952) found that 64 per cent. of 178 male rheumatoids from a busy hospital out-patient clinic reacted positively to the sheep cell agglutination test read at 18 hours, whereas only 46 per cent. of 464 females reacted in this way; this suggested that rheumatoid arthritis might not be a homogeneous disease in females. More recent observation on hospital in-patients suggests that, at this level of severity and diagnostic accuracy, rheumatoid arthritis is much more homogeneous, since positive tests were obtained in 90 per cent. of 149 males and 84 per cent. of 244 females; if only those with subcutaneous nodules were included, the proportion with positive tests rose to 100 per cent. of 62 males and 92 per cent. of 91 females.

The most recent analysis of the long-term results



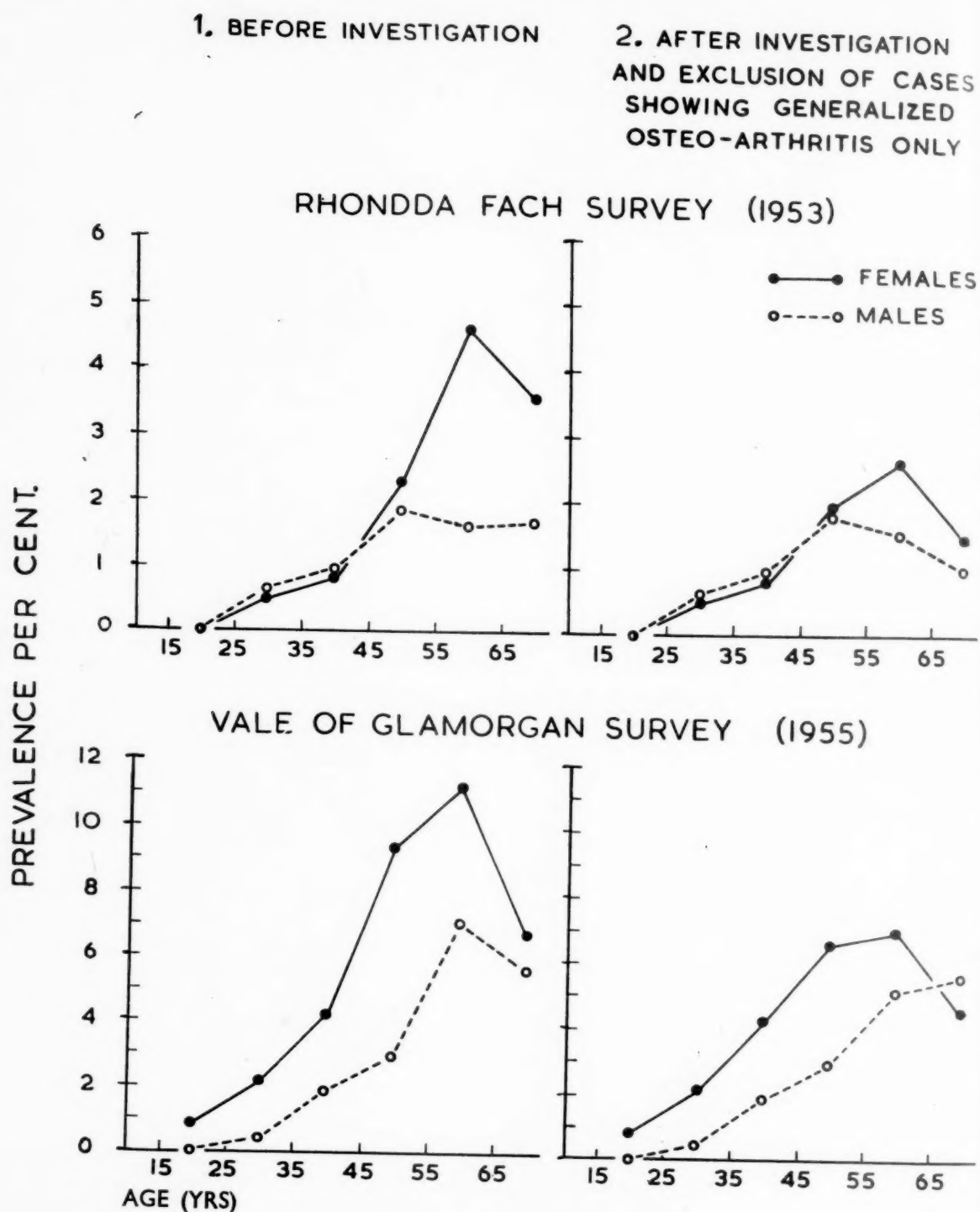


Fig. 2.—Prevalence of suspected rheumatoid arthritis in the two surveys.

of treatment of early cases of rheumatoid arthritis with cortisone and aspirin (M.R.C. and Nuffield Foundation, 1957) showed that the prognosis of patients in whom the sheep cell test was persistently negative was much better than in those with a persistently or intermittently positive test. Similar findings have been reported by Duthie, Brown, Knox, and Thompson (1957). The strict criteria which we have used in the definition of rheumatoid arthritis in these surveys of symptomatic cases would not accept the serologically negative cases of rheumatoid unless radiological signs were present; perhaps these criteria are in fact excluding a type of polyarthritis, possibly part of the spectrum of rheumatoid disease, which is more prevalent amongst women, associated with negative sheep cell agglutination tests and an absence of destructive bone changes and accompanied by a good prognosis. Such a polyarthritis may indeed ultimately show sequelae only of osteo-arthritis.

Findings like these, which are so contrary to accepted clinical experience, obviously need further investigation.

They also challenge some of our clinical concepts of rheumatoid arthritis and osteo-arthritis, and in our present state of ignorance it is clearly essential to carry out additional complete studies of random population samples so that we may obtain information about the distribution of sheep cell agglutination titres and radiological signs of both rheumatoid arthritis and osteo-arthritis at different ages. This should enable us to define more clearly the inter-relationship between clinical polyarthritis and types of radiological change on the one hand, and high agglutinating titres in the sheep cell test on the other. Furthermore, it may in time be possible to define other clinical and radiological abnormalities not at present considered rheumatoid in nature but nevertheless associated with high agglutinating titres, which may therefore represent as yet unrecognized features of rheumatoid disease.

At the same time, it would appear that both methods of study employed to date can give most useful information, that we are already in a position to assess comparative prevalence rates of rheumatoid arthritis in different populations, and that a start has been made towards establishing the geographic distribution of this important disease.

### Summary

Surveys of the prevalence of rheumatoid arthritis have been carried out in the complete populations of a mining valley, the Rhondda Fach, and of an agricultural area, the Vale of Glamorgan, in South Wales.

All subjects who passed an initial screening designed to reveal cases of polyarthritis of the rheumatoid type were asked to attend a centre for investigations. Radiographs of the peripheral joints were taken and sheep cell agglutination tests were carried out; the criteria adopted required confirmation of the diagnosis by positive radiological or serological findings.

The prevalence of rheumatoid arthritis, according to these strict criteria, was higher in the urban population, except in the oldest age groups, where it was higher in the rural population; for each radiological grade of severity of arthritis, the sheep cell agglutination test was positive at greater dilutions in the urban than in the rural subjects. These data suggest that subjects in the urban population are affected by the disease earlier, or in a more severe form, or both, but more extensive investigations are needed to establish whether this finding is generally applicable.

The expected sex difference in the prevalence of rheumatoid arthritis was present after the initial clinical screening, but largely disappeared when these strict diagnostic criteria were used. The possible implications of this finding are discussed.

We wish to record our thanks to the people of the Rhondda Fach and the Vale of Glamorgan who co-operated in these surveys; to acknowledge the help of our colleagues in both Units, particularly Dr. J. S. Lawrence, now Director of the Empire Rheumatism Council Field Unit, and Dr. J. C. Gilson, Director, and Dr. A. L. Cochrane and Mr. P. D. Oldham of the Pneumoconiosis Research Unit, for valuable discussion, advice, and statistical comment; and to thank the epidemiological and radiological teams for much of the field work involved.

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## Fréquence de l'arthrite rhumatismale dans les populations urbaine et rurale du Pays de Galles du Sud

## RÉSUMÉ

On a procédé à une enquête concernant la fréquence de l'arthrite rhumatismale parmi les populations entières de deux régions situées au Pays de Galles du Sud; une minière, Rhondda Fach, et l'autre agricole, Vale of Glamorgan.

Tous les sujets qui à un examen préliminaire avait révélé des symptômes de polyarthrite de type rhumatismal furent invités à un centre d'investigation. Ils y furent soumis à la radiographie des articulations périphériques et à la réaction d'agglutination de globules de mouton, conformément aux critères adoptés, demandant une confirmation radiologique et sérologique du diagnostic.

La fréquence de l'arthrite rhumatismale, selon ces critères strictement appliqués, fut plus grande parmi la population urbaine, sauf pour des personnes d'âge avancé pour lesquelles elle fut plus grande parmi la population rurale. Pour chaque grade radiologique de sévérité de l'arthrite, la réaction d'agglutination de globules de mouton fut positive à des dilutions plus grandes chez des sujets urbains que chez des sujets ruraux. Ces données suggèrent que les citoyens contractent la maladie plus tôt, ou sous une forme plus sévère, ou les deux; de plus amples recherches sont cependant nécessaires pour savoir si cela s'applique généralement.

Comme on avait prévu, la différence entre les sexes en ce qui concerne la fréquence de l'arthrite rhumatismale fut rencontrée après le triage clinique préliminaire, mais cette différence tendit à s'effacer dès qu'on appliqua les rigides critères diagnostiques. On discute les implications possibles de ce fait.

## Frecuencia de la artritis reumatoide en las poblaciones urbana y rural del país de Gales del Sur

## SUMARIO

Se investigó la frecuencia de la artritis reumatoide en las poblaciones completas de dos regiones del país de Gales del Sur: una cuenca minera, Rhondda Fach, y la otra agrícola, Vale of Glamorgan.

Todos los sujetos que en un examen preliminar revelaron síntomas de poliartritis de tipo reumatoide fueron invitados a un centro de investigación, y sometidos a radiografías de las articulaciones periféricas y a la reacción de aglutinación de eritrocitos de oveja, en conformidad con los criterios diagnósticos adoptados, postulando una confirmación radiológica y serológica.

La frecuencia de la artritis reumatoide, según estos criterios estrictamente aplicados, fué mayor en la población urbana, salvo para las personas de edad avanzada, respecto a las cuales esta frecuencia fué mayor en la población rural. Para cada grado radiológico de severidad de la artritis, la reacción de aglutinación de eritrocitos de oveja fué positiva a diluciones mayores en los sujetos urbanos que en los rurales. Estos datos sugieren que los ciudadanos contraen la enfermedad más temprano, o en una forma más severa, o ambos; se precisan más amplias investigaciones para ver si esto se puede aplicar generalmente.

En la clasificación clínica preliminar se encontró la diferencia anticipada entre los sexos respecto a la frecuencia de la artritis reumatoide, pero con la aplicación de los rigidos criterios diagnósticos, esta diferencia tendía a desaparecer. Se discuten las implicaciones probables de este hecho.

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## USE OF THE INTRAMUSCULAR ROUTE FOR PREDNISOLONE ACETATE THERAPY

BY

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There are several ways in which the *oral* administration of prednisolone may be unsatisfactory:

(1) Once a therapeutic dose of prednisolone has been taken for several weeks, the sudden withdrawal of therapy may have unpleasant consequences. The great majority of patients will stick to the dose ordered, but there are occasions when they may not be able to do so. The commonest involuntary withdrawal occurs during gastro-intestinal upsets, especially those due to poisoning or infection from food, when the tablets may either be vomited or passed through too quickly to be absorbed. Accidents and operations may also lead to a reduction in or cessation of therapy just when a larger dose is necessary. If it were possible to give prednisolone as a depot injection that lasted for one or a number of weeks, such complications might be avoided. A dose missed by a day or two would not result in a sudden deficiency of adrenal hormone and the fact that a dose had been missed would be known to the person responsible for giving the injection.

(2) When prednisolone is given by mouth, the stomach, duodenum, and jejunum absorb a very much higher concentration of the hormone than they normally encounter. The very low incidence of gastric complications encountered during adrenal stimulation therapy (West, 1957) suggests that the dyspepsia, stomach cramps, and peptic ulceration which are too common with oral cortisone or prednisolone therapy may result from a *local* action on the digestion tract. The giving of prednisolone by intramuscular injection might obviate much of this trouble.

(3) Prednisolone administered orally has also to pass through the liver in relatively high concentration, and two unwanted effects may result:

- (i) Some aspect of liver function may be upset.
- (ii) The liver may acquire an enhanced ability to destroy the hormone.

With regard to the former, at this Centre we have reason to suspect that amyloid formation in the liver is, to say the least, *not favourably* affected by orally administered corticosteroids. For the latter there is no supporting evidence but it is clear that an adaptation to prolonged oral corticosteroid therapy occurs somewhere.

In view of these considerations it was decided to explore the use of intramuscular prednisolone acetate therapy. At the right moment, Pfizers came forward with a very generous supply of Deltacortril (prednisolone acetate) suspension which they were anxious that we should study using the intramuscular route.

Before embarking on this investigation certain questions had to be asked and answered:

(1) *How quickly will the intramuscular prednisolone acetate produce its effects?* It was found that this depended upon the size of the dose given and the need of the patient. If a patient needed very little added cortisone-like steroid to produce a therapeutic effect, an intramuscular injection of 25 mg. prednisolone acetate (Deltacortril) would produce noticeable effects in 3 to 4 hours. If, on the other hand, the patient was accustomed to 15 mg. oral prednisolone daily, an abrupt change to a single daily injection of 25 mg. prednisolone acetate would result in a temporary relapse. The cumulative effect of the daily injections might take 3 to 4 days to restore the previous state.

(2) *Is a given dose of prednisolone acetate more, or less, effective when given by intramuscular injection?* Animal studies had suggested that it was less effective by intramuscular injection, and this is what we thought at first, but with repeated injections a

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cumulative effect became apparent and the intramuscular dose became as effective as the oral.

(3) *How long does a given injection remain effective?* This too was found to depend upon the size of the dose and the need of the patient. The problem can be reviewed in diagrammatic form. In the Figure, "A" represents a previously untreated patient with a low blood concentration of circulating adrenal hydrocortisone; "B" represents a similar patient with an average normal concentration; "C" a patient accustomed to 15 mg. oral prednisolone daily; "D" a patient accustomed to 20 mg. daily. The shape of the curve for the effective prednisolone concentration following the intramuscular injection has been deduced partly from clinical and partly from urinary corticosteroid assay findings. It will vary a little from patient to patient, the rate of absorption being no doubt affected by the vascularity of the site of the depot and by any local reaction that may occur. It will be appreciated that to treat patient "D", who is being changed from a high oral dose of prednisolone, the injections will have to be repeated every 4 to 5 days to build up an effective concentration. Patient "C" will be without benefit on the first day but will possibly be maintained on Days 2 and 3. Patient "B" will benefit for about 6 days, and Patient "A" for 2 or 3 days longer.

(4) *Will abscess formation occur?* One of the complications of the original cortisone acetate

therapy was abscess formation. The same complication has occurred with intramuscular prednisolone acetate injections, but no abscesses have resulted from injections given by our in-patient or out-patient nursing staff. The abscesses that form are clearly due to faulty technique, a technique that no doubt rarely causes trouble with other medical injections. The abscesses cause little pain or induration and may attain a great size with little tendency to point. When incised they heal readily. Staphylococci were cultured from the abscesses we encountered.

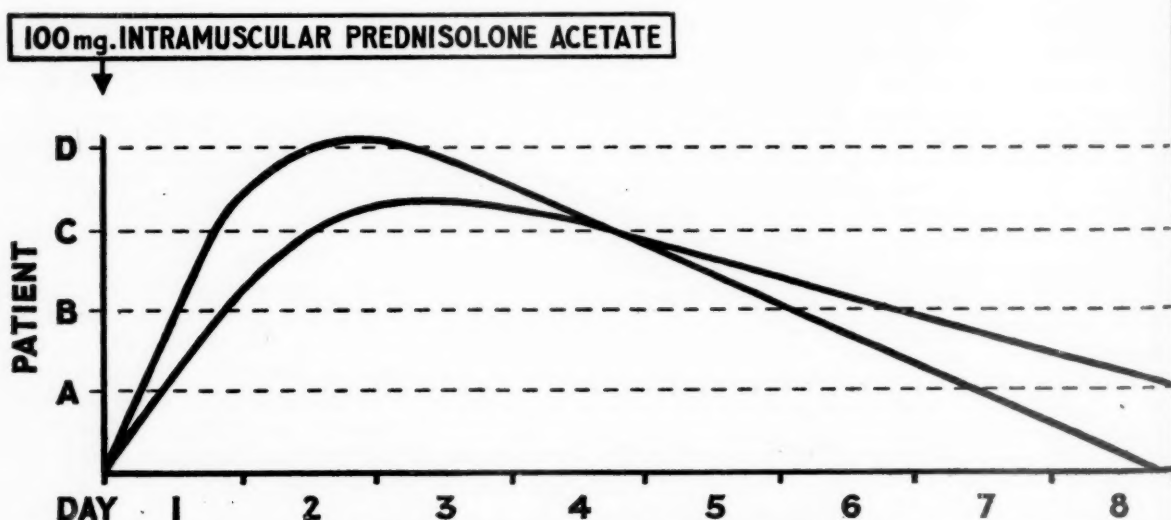
### Patients

The patients treated fell into two groups:

(a) Those with severe, long-standing disease, who had received oral steroid therapy for several years and who were in trouble from gastro-intestinal and other complications,

(b) Those who had had little or no previous steroid therapy.

To a Centre specializing in the treatment of rheumatoid arthritis the most difficult therapeutic problems gravitate from far and wide, and most of the patients treated presented difficult problems. The brief case reports which follow start with the simple and proceed to the complex problems. The letters PAIM are used to denote prednisolone acetate suspension (Deltacortril Pfizer) by intramuscular injections.



## Case Reports

**Case 1, a male aged 36**, had rheumatoid arthritis for 6 months, and was unable to continue work (he was self-employed).

He was given 80 mg. PAIM once each week for 25 weeks. He was occasionally stiff on Day 7, but otherwise without signs or symptoms of rheumatoid arthritis and able to work full time. He had no digestive disturbance.

**Case 2, a female aged 43**, had rheumatoid arthritis for 1 year, and had received phenylbutazone  $3 \times 100$  mg. for 1 year. The disease activity was widespread and her grip was too weak for her to continue at work.

She was given 80 mg. PAIM once each week for 30 weeks. She had no symptoms for 20 weeks, but now has some stiffness on Days 6 and 7. She is working normally, and has no digestive disturbance.

**Case 3, a male aged 50**, had rheumatoid arthritis for 12 years, with a long history of recurrent dyspepsia. He had previously received cortisone and prednisolone for 1 year, and his condition was unsatisfactory on 15 mg. prednisolone by mouth.

He was given 80 to 100 mg. PAIM weekly for 28 weeks, with almost complete relief of symptoms. He is working normally, and has no digestive disturbances.

**Case 4, a female aged 46**, had rheumatoid arthritis for 9 years, and myxoedema for 4 years. Prednisolone 10 mg. for 1 year had been satisfactory, but there was a previous history of duodenal ulcer.

She was given PAIM 80 to 70 mg. weekly for 25 weeks. She is symptom free, and has no digestive disturbance.

**Case 5, a male aged 56**, had rheumatoid arthritis for 5 years. Aspirin therapy (in the Aspirin/Cortisone Trial) for 4 years had ended in gross deformity, so that he was unable to work. Adrenal stimulation therapy for 15 months had restored his health and earning capacity.

Because of breathlessness on exertion (chronic bronchitis) he was given PAIM 80 mg. weekly for 13 weeks. The arthritis was well controlled but breathlessness on exertion returned, and he has now been changed to Triamcinolone.

**Case 6, a female aged 61**, had rheumatoid arthritis for 11 years, with gross deformity and much pain. Prednisolone 10 mg. orally for 4 months had given major relief but dyspepsia began and in spite of antacid therapy a gastric haemorrhage occurred.

The prednisolone was stopped, and after 2 months of dependence on others for personal needs she was given PAIM 80 mg. weekly for 25 weeks. She is now able to look after herself, and has no dyspepsia.

**Case 7, a female aged 55**, had rheumatoid arthritis for 7 years. She had received hormone therapy for 5 years, but had developed a duodenal ulcer with persistent symptoms for last 2 years.

She was given PAIM 80 mg. weekly for 25 weeks. The ulcer symptoms went immediately but returned after

several weeks. They persisted in spite of all treatment until she went on holiday, when they finally disappeared.

**Case 8, a male aged 50**, had rheumatoid arthritis for  $3\frac{1}{2}$  years. The disease was not controlled by aspirin or phenylbutazone, and he was given adrenal stimulation therapy for 15 months followed by 1 year on prednisolone 15 mg. daily. During the prednisolone therapy a gastric ulcer developed and a haemorrhage occurred; the prednisolone was continued but severe pain recurred.

He was given PAIM 40 mg. every other day and later 60 mg. every 4 days for 32 weeks. The gastric symptoms disappeared immediately but dyspepsia recurred after 8 weeks and has recurred intermittently ever since.

**Case 9, a female aged 62**, had rheumatoid arthritis for 34 years, and myxoedema for 4 years. She had had steroid therapy for 5 years, and a severe relapse occurred while she was on 15 mg. prednisolone.

She was given PAIM 60 mg. every 3 days and later every 4 days for 20 weeks. Recovery was rapid but there was some relapse after 12 weeks. She has no digestive disturbance.

**Case 10, a male aged 41**, had rheumatoid arthritis for 5 years. He had had steroid therapy for  $4\frac{1}{2}$  years, and for the last year prednisolone 12.5 to 15 mg. daily.

Weakness, dyspepsia, loss of appetite, and early signs of peripheral neuritis (in the feet and ankles) prompted a change to PAIM 40 mg. daily, which was slowly reduced to 80 mg. weekly for 42 weeks. His strength and appetite are restored, and he is back at work, but latterly epigastric pain of the duodenal ulcer type has recurred intermittently.

**Case 11, a female aged 35**, had rheumatoid arthritis for 7 years with bronchiectasis. The arthritis was widespread with gross damage in hips and knees. She had had steroid therapy for 4 years, prednisolone 15 mg. daily for the last 2 years, and had experienced recurring nausea and heartburn.

She was given PAIM 60 mg. every 3 days, for 16 weeks. There has been no digestive disturbance in spite of this excessive steroid therapy, which is to be reduced.

**Case 12, a female aged 42**, had rheumatoid arthritis for 11 years, with recurrent thyrotoxicosis. She had received steroid therapy for 7 years, and had latterly been given 10 to 12.5 mg. prednisolone.

A change to PAIM was made because of repeated attacks of abdominal pain and diarrhoea and loss of appetite. The basal metabolism rate was +25, and she was too stiff to do any housework. She received PAIM 40 mg. every other day slowly reduced to 40 mg. every 4 days for 39 weeks. She recovered rapidly and returned to work. Hypertension developed on the high dose but has fallen with decreasing dosage. On the present dose she has some stiffness on Day 4, but there is no need for anti-thyroid therapy, and no digestive disturbance.

**Case 13, a male aged 51**, had rheumatoid arthritis for 10 years. The disease was active and widespread

with much damage. He had received steroid therapy for 4 years (at a high level but the exact dose is not known). He had suffered prolonged dyspepsia.

He was given PAIM 20 mg. daily for 12 weeks. A major improvement after 4 weeks was followed by a heavy fall and a relapse, and after 12 weeks peripheral neuritis developed. There was no digestive disturbance while he was receiving PAIM.

**Case 14, a female aged 45,** had rheumatoid arthritis for 9 years. The disease was widespread with gross damage in hips and knees. She had received steroid therapy for 4½ years.

PAIM therapy was started during a period of depression; she received 60 mg. every 3 days for 30 weeks. Subjective and objective improvement was due to relief of an unrelated emotional problem. She developed hypertension because the dosage of PAIM was excessive, and was changed to Triamcinolone. There was no digestive disturbance.

**Case 15, a female aged 34,** had rheumatoid arthritis for 11 years. The disease was widespread with gross damage of hips and knees. She received steroid therapy for 4½ years, and severe gastric haemorrhage necessitated partial gastrectomy while on prednisolone. She was unable to dress or do light housework.

Because of recurring gastro-intestinal upset and vomiting she was given PAIM 40 mg. every other day for 22 weeks. The gastric symptoms disappeared at once and did not recur, and she was able to dress herself and be of use in the house and shop. The therapy was changed to Triamcinolone because of oedema of the legs, and 2 weeks later gastric symptoms recurred.

**Case 16, a male aged 40,** had severe ankylosing spondylitis for 14 years, involving the hips (which were destroyed) and knees as well as the whole spine.\* He had received steroid therapy for 6½ years, latterly 12·5 mg. prednisolone.

Severe dyspepsia, loss of appetite, impotence, and the appearance of a large amyloid liver prompted a change to PAIM 40 mg. every other day, reduced to 50 mg. every 3 days, for 45 weeks. There was a major improvement in strength, and he was able to return to work. His appetite returned and the dyspepsia disappeared. After 4 to 5 months the dyspepsia and melaena recurred, but for the last 3 months all has been well.

#### Other Findings

**Erythrocyte Sedimentation Rate.**—A fall occurred in most patients, as would be expected with the increase in effective dosage that most patients received.

**Haemoglobin.**—No significant change.

**Total White Blood Count.**—Tendency to rise.

**Strength of Grip.**—Major increase in most patients.

**Weight.**—Some rise in patients receiving more than 100 mg. PAIM each week.

\* The patient's brother had had every joint in his body and his eyes destroyed by ankylosing spondylitis and had died of amyloidosis

**Blood Pressure.**—Significant rise in Cases 11, 12, and 14 while receiving a high dosage.

**Moonface.**—Noticeable in women receiving 100 mg. or more each week.

#### Discussion

It should be emphasized again that most of the patients treated were problem cases gathered together from some 4,000 rheumatoid arthritics treated in recent years. It is apparent that, if one wants or needs to give prednisolone by intramuscular injection over prolonged periods, Deltacortril suspension (Pfizer) is suitable and convenient. The present preparation is a little bulky as it contains only 20 mg. per ml., but more concentrated suspensions that are absorbed at a suitable rate will no doubt be forthcoming. Two preparations of prednisolone containing 100 mg. per ml. have been tried, but they have been found satisfactory in only a minority of patients. In one patient a single injection of 400 mg. remained effective for more than 3 weeks. Preparations of cortisone acetate and of Triamcinolone prepared for intra-articular injection were absorbed too fast by intramuscular injection for weekly maintenance therapy.

Our experience of the difficult patients described above leaves no doubt that intramuscular prednisolone is of real value in preventing or minimizing the gastro-intestinal disturbances that occur with oral therapy. The marked improvement in health of Case 16 with a large amyloid liver on changing from oral to intramuscular prednisolone is worthy of note. It will take a year or two to find out whether intramuscular prednisolone will remain effective for a longer time than oral prednisolone. Systemically administered cortisol, produced by adrenal stimulation, certainly remains effective for a much longer period than oral cortisone acetate (West, 1957). It was hoped that, by using the intramuscular route and avoiding the liver, some of the side-effects might have been less. So far this has not proved to be the case, though there has been less weight gain than expected. The need to keep the dosage down to safe levels remains. This is easy to say but difficult to practise with the 1 per cent. of rheumatoid arthritics who run a prolonged severe course.

#### Summary

Intramuscular prednisolone acetate (Deltacortril suspension Pfizer) has been given for periods of from 16 to 45 weeks to sixteen patients suffering from severe rheumatoid arthritis. A weekly depot injection was found to be satisfactory. Certain advantages attend this route of prednisolone administration, including, in particular, a marked

lessening of gastric disturbance. Other benefits may become apparent during long-term therapy.

Grateful thanks are due to Dr. G. R. Newns and Dr. H. W. Fladee for much clinical help and to the nursing staff of this Centre for their indispensable service.

## REFERENCE

West, H. F. (1957). *Ann. rheum. Dis.*, 16, 322.

## L'acétate de prednisolone par voie intramusculaire

## RÉSUMÉ

On administre de l'acétate de prednisolone (Deltacortril suspension, Pfizer) par voie intramusculaire pendant des périodes de 16 à 45 semaines à 16 malades atteints d'arthrite rhumatismale sévère. On trouva qu'une injection de dépôt par semaine fut satisfaisante.

Cette voie d'administration de la prednisolone présente certains avantages, y compris, en particulier, une diminution marquée des troubles gastriques. D'autres avantages pourraient apparaître si l'on prolongait le traitement.

## El acetato de prednisolona por vía intramuscular

## SUMARIO

Acetato de prednisolona (Deltacortril suspensión, Pfizer) fué administrado por vía intramuscular durante periodos de 16 a 45 semanas a 16 enfermos con artritis reumatoide severa. Una inyección de depósito por semana dió resultados satisfactorios. Esta vía de administración ofrece ciertas ventajas, incluso, en particular, la disminución marcada de disturbios gástricos. Otras ventajas pudieran evidenciarse con un tratamiento más prolongado.



## SUBCUTANEOUS NODULES OF STILL'S DISEASE\*

BY

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*From the Rheumatism Research Unit, Medical Research Council, Canadian Red Cross Memorial Hospital, Taplow, and the Postgraduate Medical School, London*

The observations of Collins (1937) and of Bennett, Zeller, and Bauer (1940) established clearly the pathological differentiation of the ordinary subcutaneous nodules in rheumatic fever and in rheumatoid arthritis.

In brief, the rheumatic fever nodule is characterized by much fibrinoid material arranged in a lattice with apparently clear spaces between the strands, considerable oedema, but relatively little cellularity. What cells are present are usually fibroblasts or histiocytes; they are sparsely distributed in the meshes of oedematous connective tissue and accompanied occasionally by lymphocytes or rarely by polymorphs near the vascular "islands" (Fig. 1, opposite). There is little attempt at zoning, although vascular "islands" are a prominent feature. Finally, fibrosis is not often a conspicuous feature, and may be entirely absent.

In contrast, the rheumatoid nodule, as seen in adults, is clearly arranged in three zones. There is an outer zone of fibrosis with considerable infiltration by lymphocytes, plasma cells, sometimes polymorphonuclears, and rarely eosinophils. The innermost zone comprises necrotic debris, sometimes containing fibrinoid material but more usually a grumous granular mass with fibrin, fibrinoid, and swollen collagen fibres mixed in it, sometimes containing nuclear debris, fat globules, and cholesterol clefts. Between the inner and outer zones lies a well-orientated layer of palisade cells, fibroblasts with large nuclei forming a compact border to the necrotic centre zone (Fig. 2, opposite). While there is some overlap in their individual features, a correct histological diagnosis can be made in nearly every case (Bennett and others, 1940, give a figure of 68 correct diagnoses in 69 patients with a firm diagnosis and one wrong diagnosis in a patient in whom the clinical diagnosis was somewhat doubtful). The exceptions show a mixed picture which gives the pathologist difficulty and leads him to issue an uncertain report. This usually corresponds to

rather atypical features in the clinical presentation. It is uncommon for the pathologist who is familiar with this field to make a wrong diagnosis.

In juvenile rheumatoid arthritis, however, we have been surprised to find over the last 10 years that the nodule resembles closely that of rheumatic fever, and we have therefore surveyed all our nodule material and correlated the findings with clinical data. Apart from Findlay (1931), who illustrates a nodule from a probable case of Still's disease resembling those of rheumatoid arthritis, we have found no reference to such a surprising finding in the extensive literature on rheumatic and rheumatoid nodules (reviewed up to 1938 by Keil (1938); and more recently by Horwitz (1949)).

### Material and Methods

Material was available from the following sources:

- (1) Twelve cases of Still's disease or juvenile rheumatoid arthritis with onset at or before the age of 16 years.
- (2) 57 cases of rheumatic fever (age range 3 to 49 years, including ten cases up to 10 years and ten cases aged 21 and over, all except twelve being below the age of 16).
- (3) 22 cases of adult rheumatoid arthritis (age range 20 to 73 years, all except one being aged 37 or over).

This material was reviewed against a general background of over seventy nodule examinations at the Postgraduate Medical School (unlisted and mostly from adult patients with rheumatoid arthritis or rheumatic fever).

After formol-saline fixation, routine paraffin sections (stained with haematoxylin and eosin, thionine, periodic acid Schiff, Gomori's silver impregnation, Mallory's phosphotungstic acid haematoxylin, and occasionally by Weigert's elastin stain and Masson's trichrome method) were surveyed, and the findings were tabulated in four grades (0-3), the patient's name and clinical data being unknown. This grading was then correlated with the clinical diagnosis (based on detailed in-patient observation, serological studies, joint biopsies occasionally, and long-term follow-up), and with

\* Paper read at the IX International Congress of Rheumatic Diseases, Toronto, in June, 1957.

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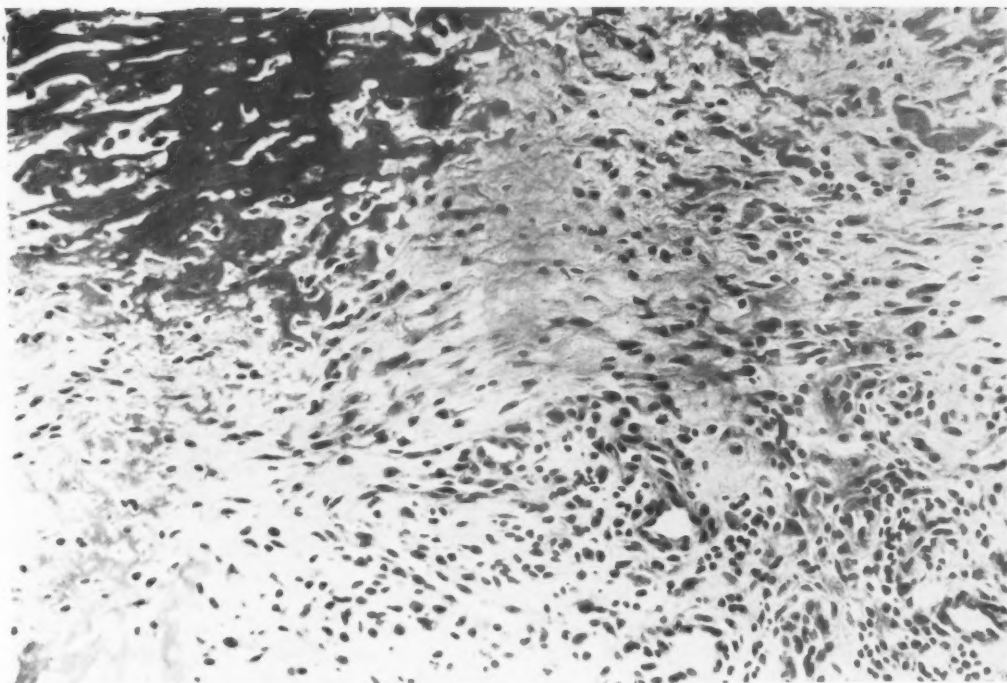


Fig. 1.—Representative area of typical nodule from a typical case of rheumatic fever in a female aged 19. Haematoxylin and eosin  $\times 163$ .

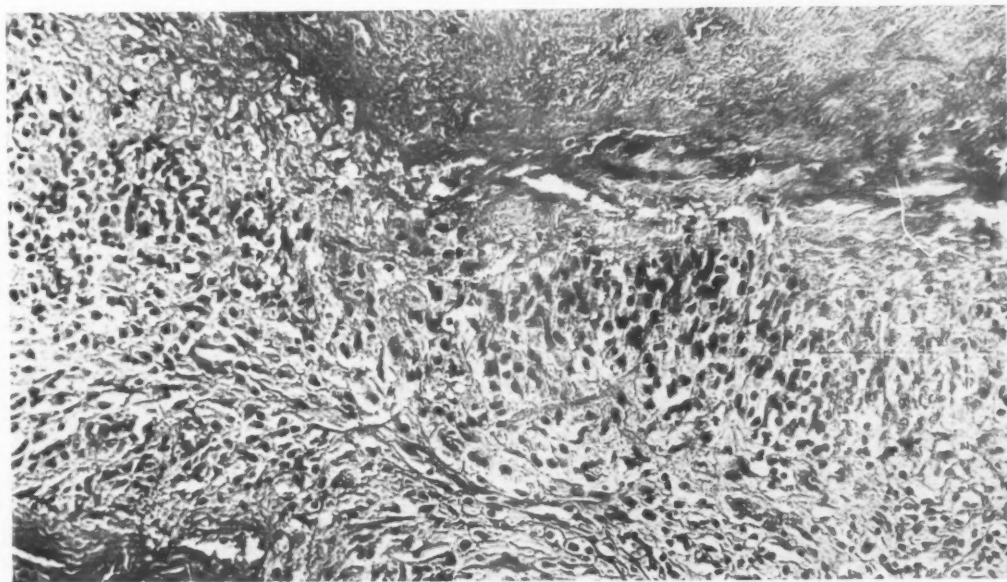


Fig. 2.—Representative area of typical nodule from a typical case of adult rheumatoid arthritis in a man aged 40. Haematoxylin and eosin  $\times 160$ .

the age, sex, duration of disease, erythrocyte sedimentation rate, and Rose-Waaler differential titre (performed by Dr. Francis Scott using a slight modification of the original method: Scott, 1952). Nine of the twelve cases of Still's disease showed gross multiple erosions at follow-up, and one of the remaining three showed a positive joint biopsy. All the last three showed repeatedly negative Rose tests and permanent residual deformities.

Results

The results are tabulated in two ways (Table 1):

- (1) The percentage of patients showing each feature in each group.
- (2) The mean grade for each feature in each group.

The only feature in the Still's disease group in which the findings resembled those in the adult rheumatoid arthritis group was fibrosis. Here, both the incidence and the mean amount of fibrosis was greater than in rheumatic fever, although not so great as in adult rheumatoid arthritis. Otherwise, the nodules of Still's disease resembled and in most instances were indistinguishable from those of rheumatic fever, showing absence of necrosis and palisading and the presence of oedema, well-marked vascular islands, and a fibrinoid lattice (Figs 3-6).

In only one instance was a diagnosis of rheumatoid arthritis made. This nodule came from the elbow of a boy aged 13 years whose rheumatoid arthritis had started at the age of 5 years. The disease was still active with an erythrocyte sedimentation rate of 71 mm./hr and a Rose-Waaler differential titre of 1 : 32. The nodule showed fibrosis (Grade 3),

some necrosis (Grade 1), and a Grade 2 palisade (Fig. 7, overleaf).

Only one other boy (aged 14, onset of arthritis at age 7 years) showed palisading, but in this case the other features (Grade 3 fibrinoid lattice, etc.) were such as to suggest a diagnosis of rheumatic fever.

By contrast, in the adult rheumatoid arthritis group, twenty out of 22 were correctly diagnosed; the two exceptions being diagnosed as "rheumatic fever" and "query rheumatic fever" respectively. The first was a girl aged 20 (onset at age 19 years, erythrocyte sedimentation rate 34 mm./hr, Rose-Waaler titre 1 : 64), who 4 years later showed typical erosions and deformities, and the second was a man aged 53 with bronchiectasis and rheumatoid arthritis of 8 months' duration (erythrocyte sedimentation rate 90 mm./hr, differential agglutination titre 1 : 64), who later showed typical bony erosions and deformities. The nodules appeared between 2 and 12 weeks before biopsy (Fig. 8, overleaf). In neither of these cases was there necrosis, fibrosis, or palisading, although fibrinoid lattice was present.

In the larger group of rheumatic fever nodules, the only case incorrectly diagnosed as rheumatoid arthritis was a boy aged 8 with typical rheumatic fever and chorea for 2½ months (raised antistreptolysin-O titre, and an erythrocyte sedimentation rate which had fallen from 33 to 15 mm./hr), who was left at the time of biopsy with residual apical systolic and diastolic murmurs. This nodule showed some fibrosis, Grade 2 necrosis, and Grade 1 palisading, with no fibrinoid lattice (Fig. 9, overleaf).

TABLE I  
HISTOLOGICAL FEATURES OF RHEUMATIC AND RHEUMATOID NODULES

Diagnosis		No. of Cases	Features Examined	Fibrosis (Grades 0-3)	Palisade (Grades 0-3)	Necrosis (Grades 0-3)	Oedema (Grades 0-3)	Vascular Islands (Grades 0-1)	Fibrinoid Lattice (Grades 0-3)	Histological Diagnosis
Rheumatic Fever		57	Percentage Present	33	19	10	74	89	91	Rheumatic Fever 56
			Mean Grade	0.4	0.3	0.1	1.2	—	2.3	Rheumatoid Arthritis 1
Rheumatoid Arthritis	Age 16 or Under at Onset	12	Percentage Present	83	17	8	75	91	100	Rheumatic Fever 11 Rheumatoid Arthritis 1
			Mean Grade	1.3	0.4	0.1	1.0	—	2.2	(DAT+ 6/12)
	Age 17 or Over at Onset	22	Percentage Present	91	87	91	14	27	59	Rheumatic Fever 2 Rheumatoid Arthritis 20
			Mean Grade	2.2	2.0	2.5	0.2	—	1.0	(DAT+ 20/21)



Figs 3-6.—Representative areas of typical nodules from four typical cases of Still's disease, aged 8, 10, 15, and 16 years. Haematoxylin and eosin.

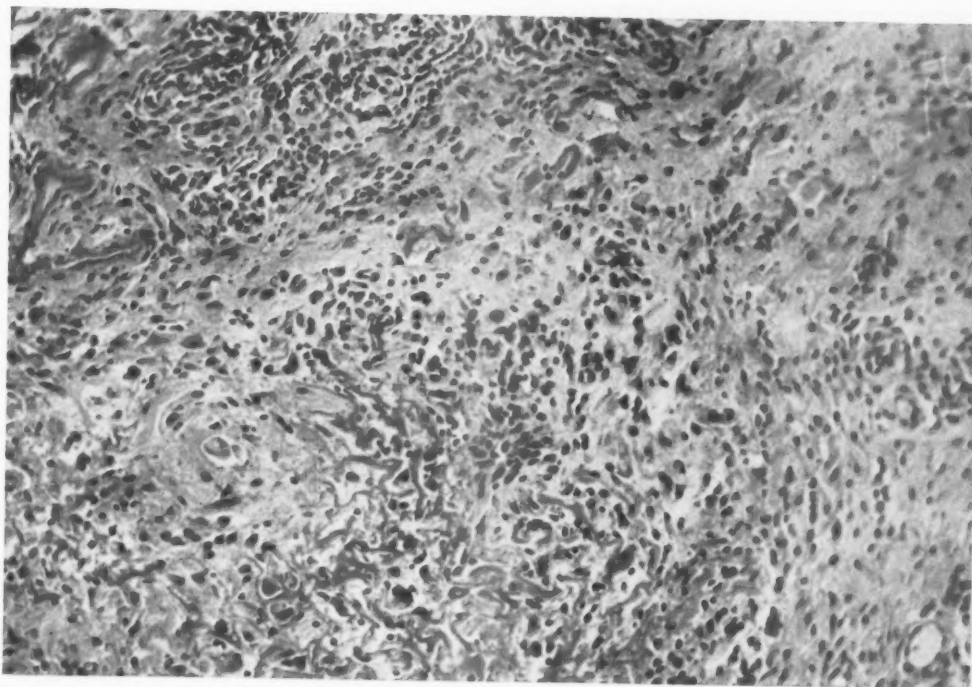


Fig. 3.—Patient aged 8 years; D.A.T. 1 : 2,  $\times 148$ .

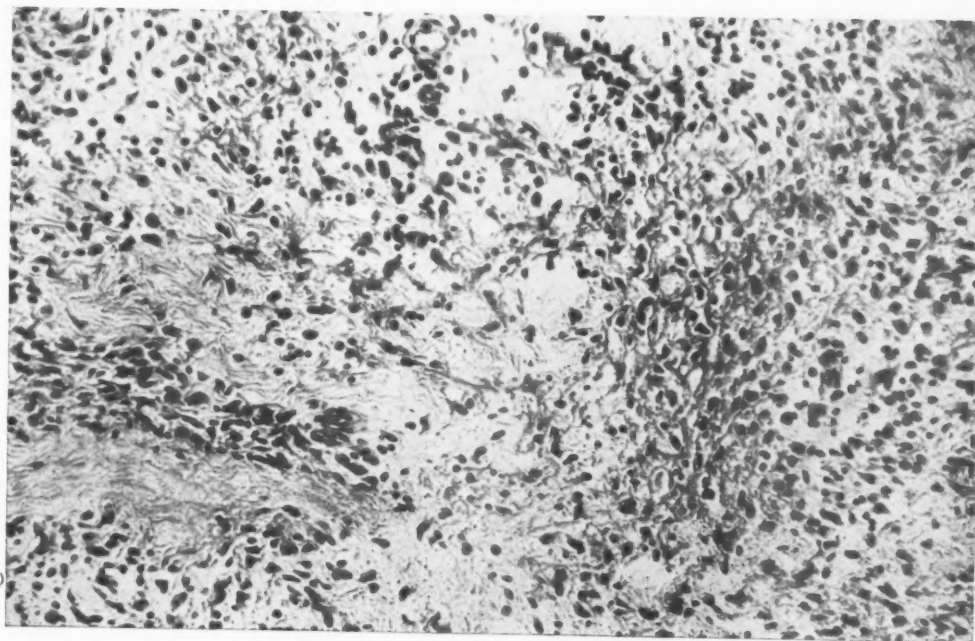


Fig. 4.—Patient aged 16 years; D.A.T. 1 : 8,  $\times 160$ .





Fig. 5.—Patient aged 15 years; D.A.T. 1 : 64.  $\times 168$ .

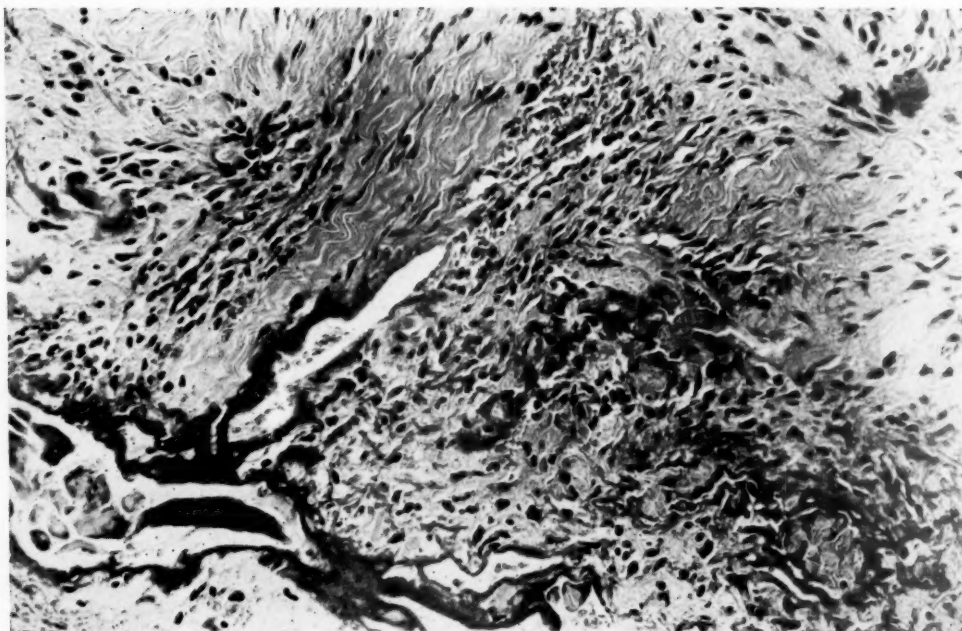


Fig. 6.—Patient aged 10 years; D.A.T. 1 : 8.  $\times 168$ .

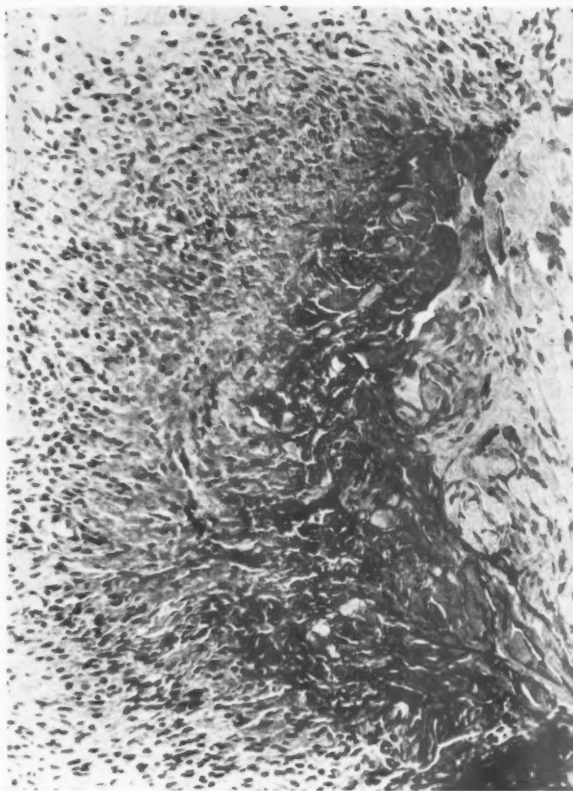


Fig. 7.—Representative area from an atypical nodule of typical Still's disease in a male aged 13 who had had rheumatoid arthritis for 8 years. Haematoxylin and eosin  $\times 140$ . (D.A.T. 1 : 32; Erosions ++.)

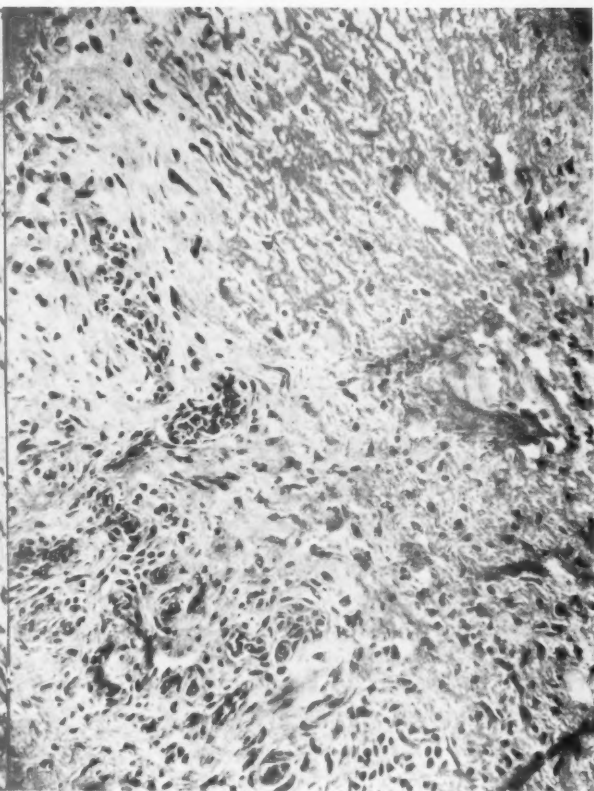


Fig. 8.—Representative area from an atypical nodule of typical adult rheumatoid arthritis in a male aged 53 who had suffered from rheumatoid arthritis for 8 months. Haematoxylin and eosin  $\times 132$ . (D.A.T. 1 : 64; Erosions +.)

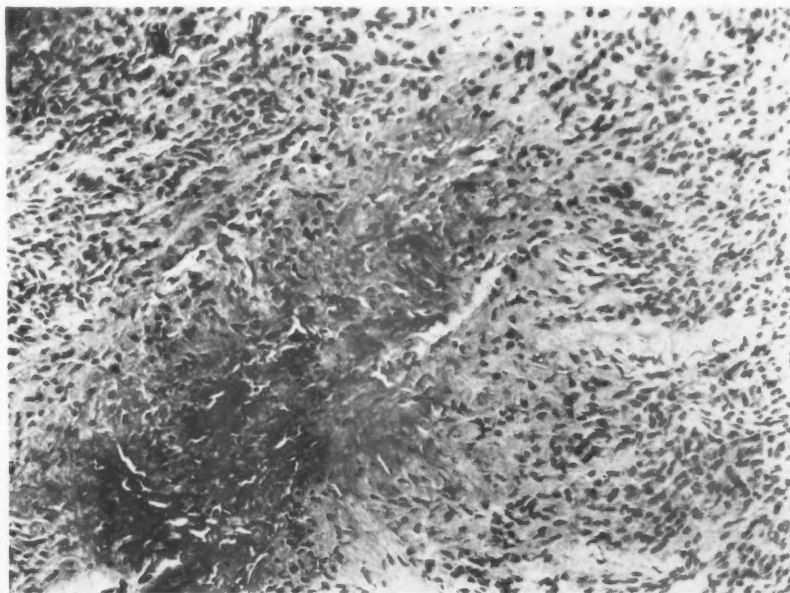


Fig. 9.—Representative area from an atypical nodule of typical juvenile rheumatic fever in a male aged 8 who had suffered from rheumatic fever for 2½ months and was left with residual valvular lesions. Haematoxylin and eosin  $\times 132$ .

Eight other patients showed Grade 1 palisading but this was associated with a bursal cavity in three and not associated with other features characteristic of rheumatoid arthritis. It should be noted that eleven of the 57 rheumatic fever nodules were biopsied at the stage of prenodule thickening (Bywaters and Horder, 1955), that is, before a definite nodule could be palpated; there were no gross histological differences between these and the fully-developed nodule except that fibrosis was absent in all but one and oedema usually present.

**Correlation with Other Features.**—Reliable data on the duration of the nodules were not available.

Within the Still's disease group, there was no obvious correlation between the various histological features nor between any one such feature and clinical data such as age, duration of disease, erythrocyte sedimentation rate, or Rose-Waaler test. The only suggestive point was that two of the three cases of long duration (7 years and over) showed the only two examples of Grade 3 fibrosis. Similar analyses for the rheumatic fever and adult rheumatoid arthritis groups gave similar negative results. The Rose-Waaler test was positive in six of the twelve cases of Still's disease (a rather higher proportion than in our total cases of Still's disease), but showed no correlation with histology. In the adult rheumatoid arthritis group the test was positive in twenty, not done in one, and negative in one.

### Discussion

The study confirms what others have noted, that it is usually easy to differentiate histologically between the nodule of adult rheumatoid arthritis and that of rheumatic fever. Nodules from cases with granuloma annulare (subcutaneous lesions) resemble fairly closely those of adult rheumatoid arthritis, as we have noted before (Bywaters, 1949). Nodules from four patients with acute lupus erythematosus and from one with an acute generalization of a disseminated discoid lupus erythematosus without rheumatoid arthritis, were variable in appearance, some resembling the lesions of rheumatoid arthritis and some those of rheumatic fever (unpublished observation); on the other hand, the nodules sometimes found in Schönlein-Henoch purpura resemble more closely those of rheumatic fever, as perhaps might be expected.

In Still's disease, however, arbitrarily separated from adult rheumatoid arthritis by an age at onset of 16 or under, the lesions closely resembled those of rheumatic fever in all but one of the twelve cases described here. If we accept the basic dictum of

morbid anatomy that similar structural appearances mean similar pathological processes, these are grounds for considering the pathogenesis of rheumatoid arthritis once again (as was done by writers in the 1920s and 1930s) as similar to that of rheumatic fever. It is not merely a question of age, since adult rheumatic fever nodules resemble rheumatic fever in children, nor is it a question of duration of disease. An alternative hypothesis would be that Still's disease is a different entity from rheumatoid arthritis as seen classically in adults. Certainly it differs in many respects: in our series of over 200 cases of Still's disease seen here over the last 19 years, pyrexia is twice as frequent as in adults, rash is six times more frequent, and splenomegaly and pericarditis are twice as frequent. On the other hand, both nodules and the presence of a positive Rose-Waaler titre are only one-third as frequent as in the rather specialized group of adults with rheumatoid arthritis seen here. Table II contrasts the findings in a group of 197 cases of Still's disease seen up to 1955 with those in a similar group of cases of adult rheumatoid arthritis seen here in the same period, but consisting of rather more unusual cases than are seen in a general hospital. However, the fact that all the manifestations of childhood disease, including that mentioned above and neck involvement, are seen from time to time in adults, and the fact that the Rose-Waaler test was positive in six out of twelve of these patients with nodules, renders it more likely that the disease is the same in both age groups and that the differing manifestations are due to the changes in "soil" with age.

TABLE II

Percentage Cases with	Rheumatoid Arthritis	
	Age 16 or Under at Onset (197)	Age 17 or Over at Onset (75)
Pyrexia .. .. .	62	33
Rash .. .. .	31	6
Splenomegaly .. .. .	26	13
Pericarditis .. .. .	8	4
Iritis .. .. .	6	5
Nodules .. .. .	9	29
Positive Rose-Waaler Test .. .. .	13	42
Normal Erythrocyte Sedimentation Rate .. .. .	15	12

As a corollary, it seems that the manifestations of rheumatoid arthritis are rather more dependent upon age change than those of rheumatic fever, although, of course, certain differences in the clinical manifestations of rheumatic fever in the young and in the old are well recognized. No differences could be seen in the patients with Still's disease who had nodules between those with and those without



a negative Rose-Waaler test. The course and outcome were variable in each of these sub-groups. However, the Rose-Waaler test was more preponderantly positive (as might be expected from analogy with the adult condition) in the group of twelve cases with nodules than in the remaining 200-odd patients with Still's disease without nodules.

### Summary

Subcutaneous nodules from 91 patients, with rheumatic fever (57 cases), rheumatoid arthritis with onset at age 16 or under (12 cases), and rheumatoid arthritis with onset at age 17 or over (22 cases), were first reviewed without reference to clinical history or diagnosis and were then correlated with the clinical data.

The nodules from the younger group of patients with rheumatoid arthritis (Still's disease) closely resembled those from patients with rheumatic fever and, apart from a slightly greater frequency of fibrosis, did not resemble those from adults with rheumatoid arthritis except in one instance. The Rose-Waaler test was positive in six out of the twelve cases of Still's disease.

In the 22 cases of adult rheumatoid arthritis (where the Rose-Waaler test was positive in all but one), only two nodules showed a picture resembling rheumatic fever rather than rheumatoid arthritis.

The implications of these findings are discussed.

We are grateful to Dr. Francis Scott for the Rose-Waaler titrations and to Mr. P. J. Fiske for the microphotographs.

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### Nodules souscutanés dans la maladie de Still

#### RÉSUMÉ

On étudia les nodules souscutanés de 91 malades, atteints de rhumatisme articulaire aigu (57 cas), d'arthrite rhumatismale ayant débuté à l'âge de 16 ans ou en dessous (12 cas) et d'arthrite rhumatismale ayant débuté à l'âge de 17 ans ou plus (22 cas). Les résultats furent d'abord considérés en dehors des antécédents cliniques et diagnostiques et rapportés ensuite aux données cliniques.

Les nodules des malades jeunes atteints d'arthrite rhumatismale (maladie de Still) ressemblaient de près à ceux des malades atteints de rhumatisme articulaire aigu et, à l'exception de la fibrose un peu plus fréquente, ne ressemblaient pas à ceux des adultes atteints d'arthrite rhumatismale, sauf dans un cas. La réaction de Rose-Waaler était positive dans six sur douze cas de maladie de Still.

Dans 22 cas d'arthrite rhumatismale adulte (avec la réaction de Rose-Waaler positive dans tous les cas, sauf un), deux nodules seulement présentaient un tableau ressemblant celui rencontré dans le rhumatisme articulaire aigu, plutôt que dans l'arthrite rhumatismale.

On discute les implications de ces résultats.

### Nódulos subcutáneos en la enfermedad de Still

#### SUMARIO

Se estudiaron los nódulos subcutáneos de 91 enfermos con reumatismo articular agudo (57 casos), artritis reumatoide empezada a la edad de 16 años o antes (12 casos) y artritis reumatoide empezada a la edad de 17 años o después (22 casos). Se consideraron los resultados primero fuera de los antecedentes clínicos y diagnósticos y luego en relación a los datos clínicos.

Los nódulos de los enfermos jóvenes con artritis reumatoide (enfermedad de Still) se parecieron mucho a los de los enfermos con reumatismo articular agudo pero, con excepción de fibrosis algo más frecuente, no se parecieron a los nódulos de los adultos con artritis reumatoide, salvo en un caso. La reacción de Rose-Waaler fué positiva en seis de los doce casos de enfermedad de Still.

En 22 casos de artritis reumatoide adulta (con la reacción de Rose-Waaler positiva en todos los casos, salvo uno) dos nódulos sólo presentaron un cuadro encontrado en el reumatismo articular agudo.

Se discuten las implicaciones de estos datos.



## RHEUMATOID DISEASE IN THE LARYNX AND LUNG

BY

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Visceral manifestations of rheumatoid disease have recently received considerable attention. Lesions in the larynx, lung, and heart are of clinical importance. The object of this paper is to report one example of severe laryngeal involvement and another with unusual pulmonary lesions. The histochemical properties of these lesions are compared with those of a histologically typical rheumatoid nodule.

### Case Reports

#### Case 1. Rheumatoid Disease of the Larynx

A woman aged 32 was admitted to hospital on February 10, 1957, with dyspnoea which had been present for 3 weeks and had become worse in the last 3 days. She had an unproductive cough. A similar attack, lasting one week, had occurred 6 weeks before admission.

Rheumatoid arthritis had been present since 1948; an arthrodesis of the left knee was done in 1951 because of severe flexion contracture. At this time there was facial hirsuties and a palpable spleen; the blood haemoglobin was 11.1 g. per 100 ml., the lowest white blood count was 3,700 per cu.mm. with 65 per cent. polymorphonuclear neutrophil leucocytes, and the erythrocyte sedimentation rate (Wintrobe) was 30 mm. in the first hour (corrected).

At the final admission she was thin, pale, and slightly cyanosed. Breathing was noisy and laboured. There was little lateral movement of the chest; breathing was largely accomplished by the accessory muscles of respiration. Laryngoscopy showed adduction of both cords: the left did not move and there was limitation of adduction on the right side. The interarytenoid region was oedematous. Examination of the lungs revealed diffusely scattered inspiratory and expiratory rhonchi. The respiratory rate was 40 per min., pulse rate 120 per min., temperature 99° F., and blood pressure 130/90 mm. Hg.

The patient was placed in a steam tent, but died suddenly 3 hours after admission. A tracheostomy was not made.

She had been treated with cortisone in hospital in 1951, and had had cortisone and Neomycin ointment to the eye a few months before death. During the last 2 days of life she was treated with Achromycin.

**Necropsy.**—The soft tissues of the larynx were oedematous but the glottis was patent. The mucosa of the larynx and trachea was yellow-red and covered by a small

quantity of frothy fluid. The left vocal cord was swollen and shortened; the space between it and the vocal fold was reduced so that the orifice of the sinus of the larynx was occluded. The changes in the right cord were similar but less severe. The perichondrium of the cricoid stripped easily to reveal a median posterior necrotic defect of cartilage, about 0.4 cm. in diameter.

The lungs were firm and oedematous and contained areas of consolidation in the lower lobes. Fibrous adhesions obliterated both pleural sacs. The heart showed a moderate degree of right ventricular hypertrophy; the atria, valves, left ventricle, and coronary arteries showed no important abnormality.

The spleen weighed 518 g. and had a dark purple-red cut surface in which Malpighian bodies were conspicuous. There was moderate enlargement of cervical, axillary, mediastinal, abdominal, and inguinal lymph nodes. A large grey-brown thymus was present (38 g.).

The hip joints, right knee, ankles, and right elbow were ankylosed; there was an arthrodesis of the left knee. The adjacent muscles were conspicuously wasted. The proximal interphalangeal joints showed characteristic "spindling" deformity; the fingers were deviated to the ulnar side. The wrist joints were swollen.

The body weighed 38 kg. and measured 160×38 cm. The breasts were small. Sparse long hairs were present on the chin and upper lip; axillary and pubic hair was of normal distribution.

**Histological Examination.**—The larynx was hemisected longitudinally. Serial sections were made of the right half (Fig. 1, opposite) and also of a block taken from the left side through the full thickness of the posterior half of the vestibule of the larynx. This block was intended to include the left crico-arytenoid joint.

The right crico-arytenoid joint contained a few flakes of fibrin (Fig. 2, opposite) and a fold of synovium. Foci of granulation tissue in places replaced the lining of the joint, and adjacent areas of cartilage showed areas of bone absorption and also a few small areas of deposition of newly-formed woven bone.

Sections of the left side of the larynx (Fig. 3, opposite) did not reveal the arytenoid cartilage which had, apparently, been replaced by a dense chronic inflammatory infiltrate containing numerous plasma cells, lymphocytes, histiocytes, fibroblasts, scanty neutrophil polymorphonuclear leucocytes, and occasional giant cells.



Fig. 1.—infiltrate and cricoid



Fig. 1.—Longitudinal section of right side of larynx (Case 1), showing infiltration of aryepiglottic fold and relative positions of arytenoid (A) and cricoid (C) cartilages. (E=epiglottis, T=thyroid cartilage.) Haematoxylin and eosin.  $\times 2.5$ .

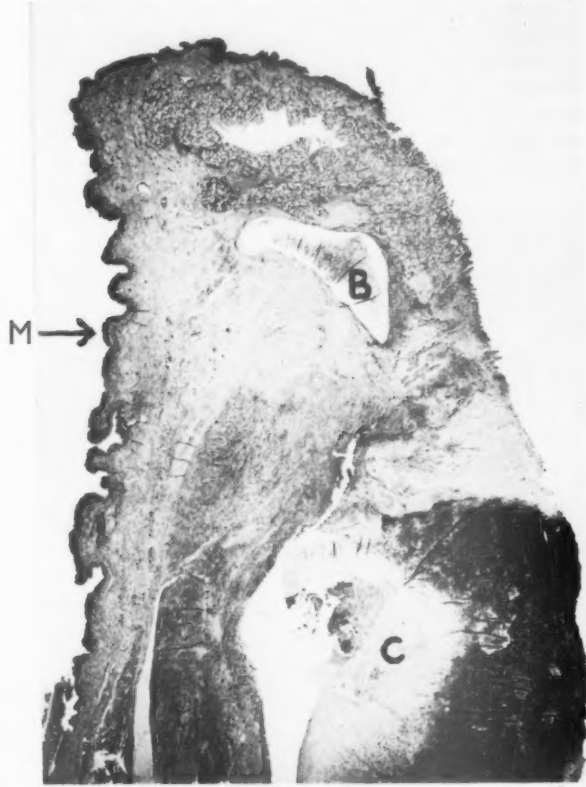


Fig. 3.—Longitudinal section of postero-lateral wall of laryngeal vestibule (Case 1), showing corniculate (B) and cricoid (C) cartilages, oesophageal mucosa (M), and heavy inflammatory infiltrate around posterior necrotic defect in cricoid. Haematoxylin and eosin.  $\times 3.5$ .

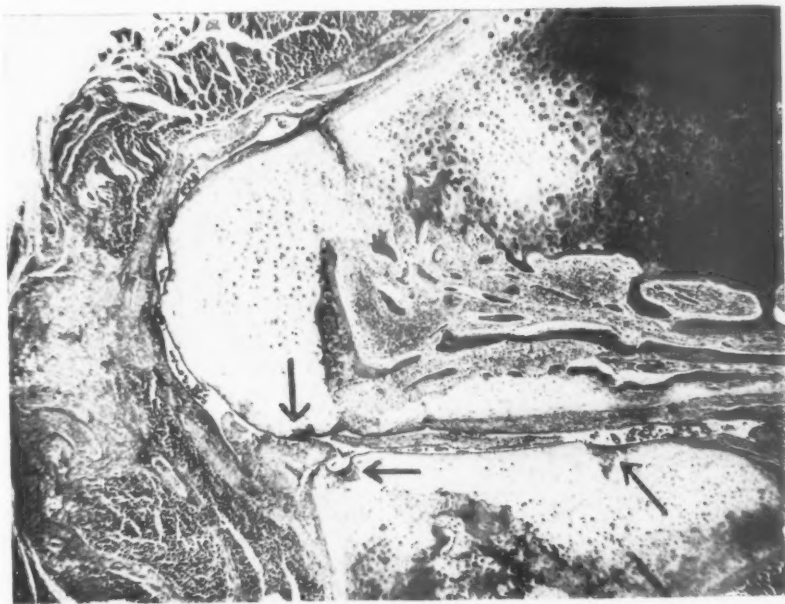


Fig. 2.—Right crico-arytenoid joint (Case 1), showing flakes of fibrin and synovial folds in joint space and granulation tissue (arrowed) invading cartilage. Haematoxylin and eosin.  $\times 17$ .

This exudate extended around the adjacent cricoid cartilage, which was invaded by similar granulation tissue containing small islands of cartilage (Fig. 4) clearly demonstrated by its metachromatic staining with 1 per cent. toluidine blue. A small area of the adjacent cartilage was necrotic. The corniculate cartilage appeared normal.



Fig. 4.—Case 1, postero-superior edge of cricoid cartilage (C), showing invasion of cartilage by granulation tissue (G), with isolated islands of cartilage (arrowed). Toluidine blue.  $\times 16$ .

The inflammatory infiltrate on both sides of the larynx extended from the epiglottis to the origin of the trachea, involving all the soft tissues including the pharyngo-oesophageal mucous membrane. The infiltrate was most severe around the cricoid cartilage on the left, resulting in considerable damage to the voluntary muscles, many of the fibres of which were represented by giant cells (Fig. 5). Ill-defined, brightly eosinophilic granular areas with the staining properties of fibrinoid were present in this region.

The spaces between the trabeculae in the ossified areas of the arytenoid and cricoid cartilages were filled with vascular connective tissue containing plasma cells and lymphocytes.

Areas of recent bronchopneumonia were present in sections of lung, together with a severe degree of oedema and areas of intra-alveolar haemorrhage. Many bronchioles were surrounded by a slight chronic inflammatory

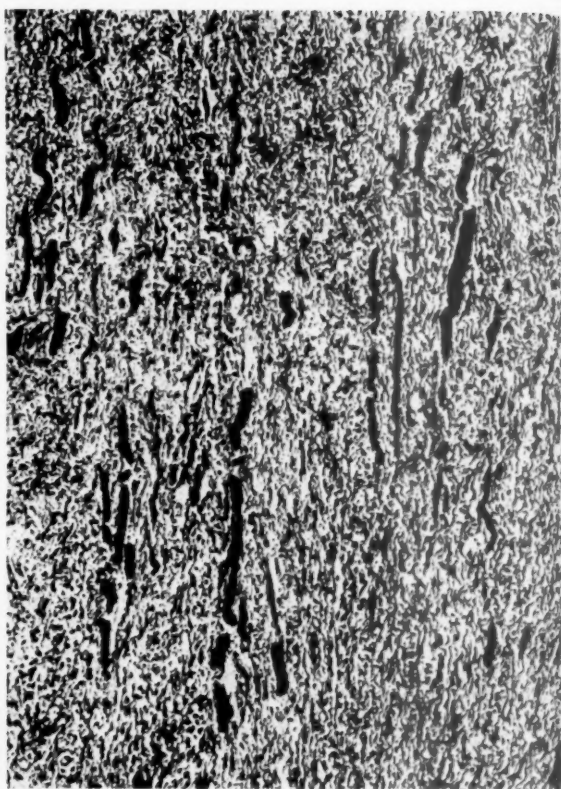


Fig. 5.—Left side of larynx, showing destruction of voluntary muscle (Case 1). Muscle fibres black. Mallory's phosphotungstic acid haematoxylin.  $\times 90$ .

cell exudate including occasional foreign body giant cells.

In the heart small perivascular foci of lymphocytes were present in the ventricular septum. Foci of lymphocytes and plasma cells were found in sections of skeletal muscle.

#### Case 2. Cardiac and Pulmonary "Rheumatoid Disease"

A man aged 57 was brought in dead, having collapsed one hour before whilst riding on a bus. He had recently suffered pain in the chest on exertion. Rheumatoid arthritis had been present for 21 years. He had last seen his doctor 5 years before, and had not apparently ever been treated with cortisone.

**Necropsy.**—A severe degree of rheumatoid arthritis was present in both hands and wrists. The forearms were wasted and both elbow joints swollen. A subcutaneous node (2 cm. diameter) was found over the right olecranon process. Other joints were involved to a less severe degree.

The aortic valve was incompetent, the free margins of the cusps being thickened and fused at the commissures (Fig. 6, opposite); there was no calcification of the valve cusps. The left ventricle was moderately dilated and hypertrophied (the heart weight 480 g.).

The lungs were emphysematous and contained diffuse tiny subpleural cysts in all lobes (Fig. 7, opposite).



Fig. 6.—Aortic valve (Case 2), showing thick free borders of cusps and commissural fusion.

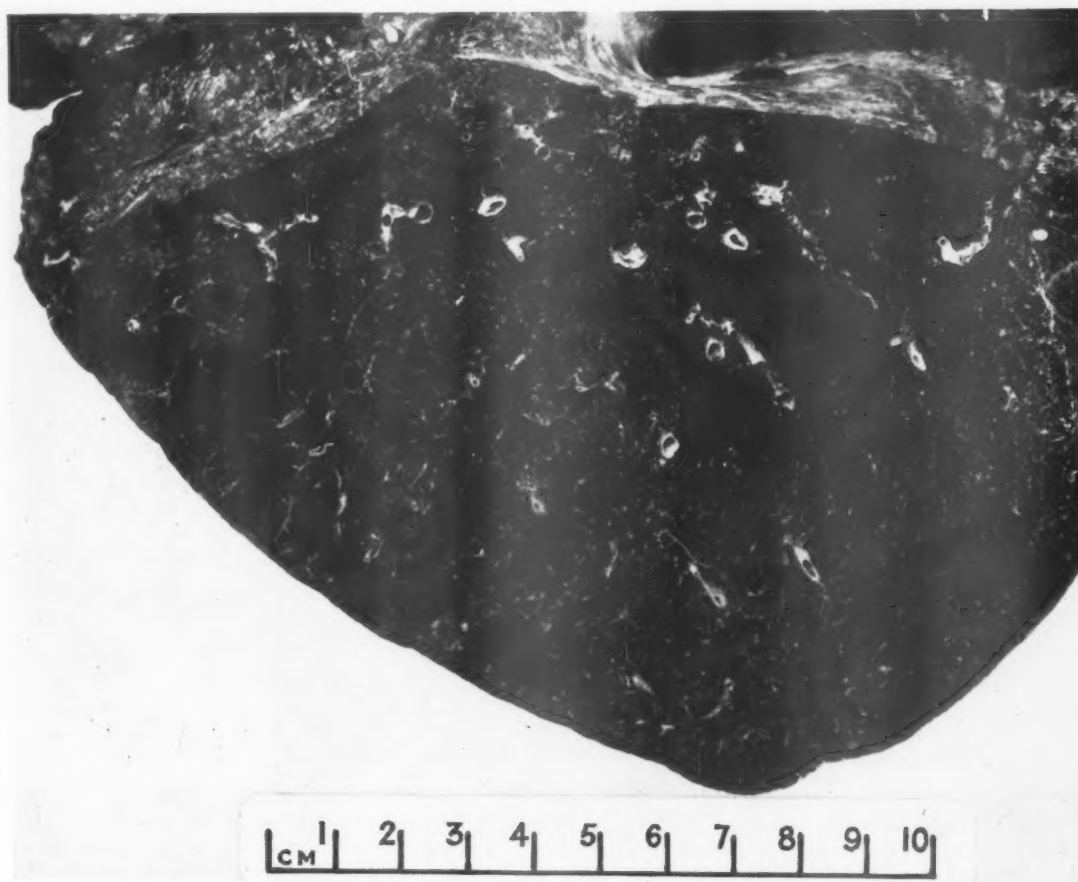


Fig. 7.—Subpleural pulmonary cysts (Case 2).



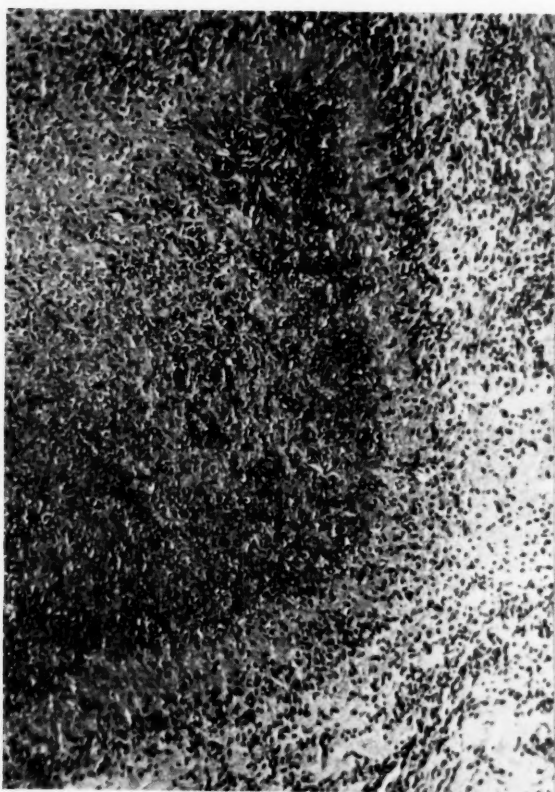


Fig. 8.—Palisades of histiocytes in subcutaneous node (Case 2).  
Haematoxylin and eosin.  $\times 75$ .

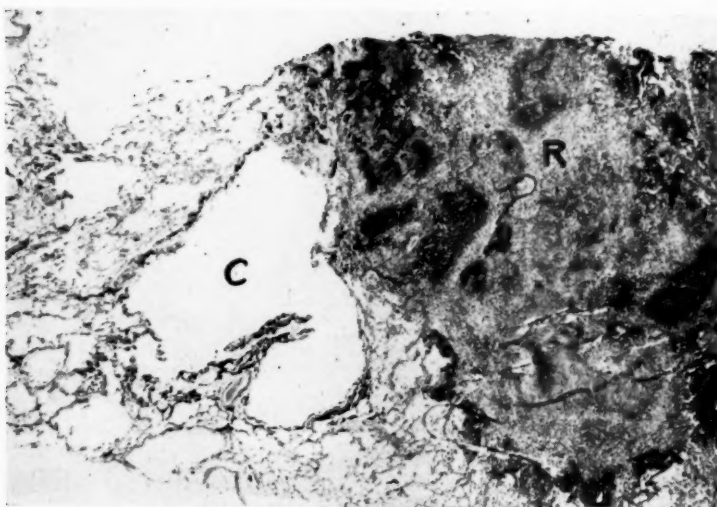


Fig. 10.—Rheumatoid granuloma (R), with adjacent cyst (C) in lung (Case 2).  
Haematoxylin and eosin.  $\times 9$ .

The spleen weighed 230 g. Lymph nodes were enlarged in the neck, mediastinum, axillae, abdomen, and groins. Other organs showed no important abnormality.

**Histological Examination.**—A section of the subcutaneous node showed the typical appearance of rheumatoid disease: areas of necrosis containing fibrinoid material were surrounded by palisades of histiocytes (Fig. 8). Similar nodules were present in a section of lung taken from the left upper lobe (Fig. 9). The cysts in the lung were lined by connective tissue containing conspicuous groups of lymphocytes and smooth muscle; most had no epithelial lining. They were probably derived from alveolar ducts (Cunningham and Parkinson, 1950). It was not possible to determine whether the cysts were derived by granulomatous destruction of the lung tissue because "active" rheumatoid lesions were scanty.

Superficial fibrinoid necrosis bordered by palisaded histiocytes was present in the section of aortic valve (Fig. 10).



Fig. 9.—Aortic valve (Case 2), showing "rheumatoid lesion" (arrowed) on inner surface of cusp. Haematoxylin and eosin.  $\times 3$ .

### Histochemical Findings in Cases 1 and 2

Comparison of the well-defined nodular lesions in Case 2 with the diffuse areas of fibrinoid material in the larynx was difficult. Nevertheless the histochemical findings were similar. The lesions contained abundant protein as shown by the tetrazo method (Danielli, 1947) and were much more intensely stained than the surrounding tissues. Ribonucleic acid and deoxyribonucleic acid were demonstrated in the lesions by pyronin and the Feulgen method respectively. The Feulgen-positive material was present mainly as nuclear remnants in the peripheral zone of inflammatory cells of the rheumatoid lesion (Case 2).

Fibrinoid material was P.A.S. positive. Permanganate paraldehyde fuchsin (Gomori, 1950) did not stain the fibrinoid material, but faint staining was obtained with sudan black.

The histochemical findings show that the lesions in both cases contain similar material which would appear to be a muco- or glyco-protein, probably derived from dead cells. The peripheral Feulgen-positive fragments in the lesions in Case 2 are most likely to be nuclear remnants.

### Discussion

Although rheumatoid disease has previously been described in the larynx, the precise site of the lesion and its histological appearance has not been clearly defined. Some authors (Montgomery, Perone, and Schall, 1955; Pearson, 1957; Copeman, 1957; Baker and Bywaters, 1957) regard the crico-arytenoid joint as the principal site of involvement. However Megighian (1955) has described diffuse degeneration of laryngeal, nasal, and auricular cartilage, with adjacent fibrinoid necrosis in biopsy specimens from a case of rheumatoid arthritis. Localized nodules of rheumatoid disease have not been described in the larynx itself though nodular involvement of the epiglottis has been reported (Raven, Weber, and Price, 1948).

The lesion in Case 1 has some features in common with that described by Megighian. There was a diffuse infiltration of laryngeal tissues by chronic inflammatory cells with some fibrinoid necrosis. Associated with this was destruction of cartilage, clearly demonstrable in the cricoid; the left arytenoid had apparently disappeared.

Fragments of fibrinoid material were present in the cricoarytenoid joint space of the opposite side. The joint was, however, relatively unaffected as compared with other parts of the larynx which showed a severe degree of inflammation of the soft tissues and considerable muscle destruction.

Laryngeal obstruction which necessitates tracheostomy is occasionally seen in patients with rheumatoid arthritis, and has been attributed to arthritis of the cricoarytenoid joint. In Case 1, the laryngeal obstruction could be explained by muscle destruction alone. Complete paralysis of the left vocal cord was probably due to the severe degree of inflammation and destruction of the arytenoid cartilage rather than to joint involvement.

Text-books of laryngology describe chronic hyperplastic laryngitis (Ellis, 1951; Scott-Brown, 1952; Thomson and Negus, 1955), considering "rheumatic disease" as one of many causative factors. The laryngeal lesion in Case 1 may be described as hyperplastic laryngitis. The diffuse chronic inflammatory infiltration of the larynx associated with rheumatoid arthritis, and the presence of material similar histochemically to that found in the rheumatoid nodule, strongly suggest that the laryngeal lesion itself is rheumatoid in origin. On the other hand, the fibrinoid degeneration may be the response of a rheumatoid patient to non-specific chronic laryngitis. It is possible that the diffuse inflammatory lesion is a precursor of rheumatoid crico-arytenoiditis, but the evidence from this case does not support such a view.

The clinical diagnosis of rheumatoid arthritis of the crico-arytenoid joint has been based on the following findings: local tenderness between the thyroid and cricoid cartilages, a variable amount of oedema and redness in the arytenoid and pre-arytenoid area, and pain on manipulation of the arytenoids (Montgomery and others, 1955; Copeman, 1957; Baker and Bywaters, 1957). It is probable that similar signs would have been demonstrable in Case 1.

Sections of rheumatoid and normal larynx demonstrated the lateral position of the joint space and the anterior position of the arytenoid cartilage. Failure to appreciate this anatomical feature may lead to the erroneous histological diagnosis of forward subluxation of the arytenoid.

Specific rheumatoid lesions in the heart valves (Baggenstoss and Rosenberg, 1941, 1944; Gruenwald, 1948; Bywaters, 1950; Bevans, Nadell, Demartini, and Ragan, 1954; Ellman, Cudkowicz, and Elwood, 1954; Valaitis, Pilz, and Montgomery, 1957), nodular lesions in the lung (Raven and others, 1948; Bevans and others, 1954; Christie, 1954; Ellman and others, 1954; Maher, 1954; Skogrand, 1956), nodular lesions in the lung in association with pneumoconiosis (Gough, Rivers, and Seal, 1955) and cystic lesions in the lung (Hart and Mackenzie, 1955; Dixon and Ball, 1957) are well-recognized features of rheumatoid disease and serve to empha-

size the systemic nature of the disorder. The association of pulmonary cystic changes with "rheumatoid nodules" has not, so far as we are aware, been reported.

### Summary

(1) Extensive inflammatory infiltration of the larynx, with destruction of cartilage, leading to death from respiratory obstruction, is described in a patient with rheumatoid arthritis.

(2) The diffuse nature of the rheumatoid lesion in the larynx is emphasized.

(3) The unusual association of cystic and nodular "rheumatoid" lesions in the lung are reported in another case.

(4) The histochemical features of lesions in the larynx and lung are found to be similar to those in a juxta-articular "rheumatoid nodule".

We are grateful to Dr. A. M. Barrett for his advice and criticism, and to Dr. L. C. Martin and H.M. Coroner of the City of Cambridge for permission to publish these case reports. Mr. S. W. Patman prepared the photomicrographs.

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### Maladie rhumatismale du larynx et des poumons

#### RÉSUMÉ

(1) On décrit un cas d'arthrite rhumatismale accompagnée d'une infiltration inflammatoire étendue du larynx, avec destruction du cartilage, menant à la mort due à l'obstruction respiratoire.

(2) On souligne la nature diffuse de la lésion rhumatismale du larynx.

(3) On rapporte un autre cas, peu commun, de lésions cystiques et nodulaires "rhumatismales" dans le poumon.

(4) On trouve que les caractères histo-chimiques des lésions laryngées et pulmonaires sont similaires à celles des "nodules rhumatismaux" juxta-articulaires.

### Enfermedad reumatoide en la laringe y en el pulmón

#### SUMARIO

(1) Se describe un caso de artritis reumatoide asociada a una infiltración inflamatoria extensa de la laringe, con destrucción del cartilago, conduciendo a la muerte por obstrucción respiratoria.

(2) Se subraya la naturaleza difusa de la lesión reumatoide de la laringe.

(3) Se relata un otro caso, poco común, de lesiones císticas y nodulares "reumatoides" en el pulmón.

(4) Los caracteres histo-químicos de las lesiones laringeas y pulmonares reveláronse similares a las de los "nódulos reumatoides" juxta-articulares.

## RECURRENT ATTACKS OF ACUTE RHEUMATISM IN SCHOOL-CHILDREN

BY

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The recurrent attack of acute rheumatism is a paediatric and public health problem which has received increasing attention since the efficacy of specific prophylaxis has become well-recognized. One of the recommendations of the recent Report of the Rheumatic Fever Committee of the Royal College of Physicians (1957) was:

"In individuals known to have had rheumatic fever, the administration of penicillin to prevent recurrences due to infection resulting from casual exposure to beta-haemolytic streptococci should be continued without interruption for a period of five years or until leaving school, whichever is the longer."

Hitherto, data bearing on problems such as this have been derived mainly from American sources. This paper presents information relating to recurrent episodes of acute rheumatism observed in Cardiff school-children during the years 1931-50, before specific prophylaxis was practised locally on a wide scale.

The data on which the findings are based and the method of the inquiry have already been described in detail (Hitchens, 1956). The record cards of all children who attended the school rheumatism clinic (which has always been closely associated with the local Department of Paediatrics), during the 20-year period 1931-50 were scrutinized and allocated in retrospect to appropriate diagnostic categories. As far as possible, the criteria used were those originally proposed by Duckett Jones (1944), as modified for the purposes of the M.R.C. Cortisone Trials. Two categories of acute rheumatism were distinguished:

- (1) Acute rheumatism with evidence of cardiac damage; and established rheumatic heart disease.

- (2) Acute rheumatism with no definite evidence of cardiac involvement.

Originally, the main purpose of the inquiry was to define accurately in an epidemiological context the trend of morbidity from the disease as it occurred in Cardiff. At the same time, however, the opportunity was taken to abstract from the record cards additional items of information. Analyses based on those relating to recurrent episodes are now presented as follows:

- (1) Proportion of rheumatic children experiencing recurrent episodes during observation.
- (2) Type of recurrent episode related to type of initial manifestation.
- (3) Annual risk of a first recurrent attack according to length of history after onset.
- (4) Risk of a recurrent episode according to age.
- (5) Relation between recurrent episodes and permanent cardiac damage.
- (6) Trend in the frequency of recurrent episodes over the twenty-year period.
- (7) Seasonal occurrence.
- (8) Relation of recurrence rates with a socio-economic index.

As indicated elsewhere (Hitchens, 1956), the second rheumatic group distinguished in the inquiry (children without definite evidence of heart disease) presented unsatisfactory features from a statistical point of view: exact diagnostic ascertainment was both more difficult and less complete; and accurate retrospective diagnostic classification was also much more difficult. Consequently, the present analyses relate only to the first group: those children who showed evidence of heart disease at some time during the observation period. The only exception is under the seventh heading, where an analysis of



the second group is shown in order to amplify an unexpected finding.

The present analyses are based, for the most part, on the experience of all children *who entered observation* in the years 1931-50 (*i.e.* they are not confined to those whose illnesses *began* in that period). The sixth and seventh headings include also the segment of experience from 1931 onwards, contributed by children who entered observation before that year.

A limitation of the data in relation to the present purpose must be mentioned at the outset. Necessarily, analyses were based on experience while *patients were under observation*. A substantial proportion were not seen until one year or more after the onset of rheumatism, and others were lost sight of for one reason or another before reaching school-leaving age. The present results, therefore, are not necessarily representative of children with rheumatic heart disease generally. On the other hand, these circumstances are common to most cardio-rheumatism clinics, and there is no reason to believe that any statistical bias resulting detracts from the significance of certain of the findings in the context of clinical practice.

### Method

For the present purpose, a "recurrent attack" is defined as one or more major manifestations of acute rheumatism occurring after a period of not less than three months following the end of the previous acute manifestation(s) of the disease.

Two types of index are employed: Recurrence Rate (Persons) based on the number of children who experienced an episode; and Recurrence Rate (Attacks) based on the number of episodes occurring. The denominator in each case is the number of person-years observation.

These rates have been employed in three distinct ways:

- (i) for total observation periods;
- (ii) for the individual calendar years of the period;
- (iii) for the individual years of life of a group of children while they were under supervision.

The method of computation and the small numerical discrepancies which result, as between one method and another, are briefly mentioned in the appendix.

### Results

(1) **Frequency of Recurrent Attacks.**—Table I shows a distribution of children according to the number of recurrent episodes suffered. Some 38 per cent. of boys and 32 per cent. of girls had one or more recurrences during observation. Statistically,

the sex difference is not significant and, when account is taken of period of observation, the rates are very similar for boys and girls.

TABLE I  
DISTRIBUTION OF RHEUMATIC CHILDREN ENTERING OBSERVATION 1931-50 BY NUMBER OF OBSERVED RECURRENT EPISODES, AND RECURRENCE RATES, BY SEX

Recurrent Episodes	Boys		Girls	
	No.	Per cent.	No.	Per cent.
None	118	62.4	191	68.0
1	52	27.5	55	19.6
2	16	8.5	29	10.3
3 or more	3	1.6	6	2.1
Number of Children	189		281	
Number of Recurrences	93		135	
Person-Years Observation	713.0		990.0	
*Recurrence Rate	Persons	10.0	Persons	9.1
	Attacks	13.0	Attacks	13.6

\* Per 100 person-years observation

Length of history at entry into observation might be expected to influence the observed recurrence rates. Table II compares rates for children coming under supervision within one year of onset (the great majority of whom were seen either at onset or shortly afterwards), with rates for those first seen after a longer interval. For boys, the figures are virtually the same, but for girls there is, in fact, a difference—those with a longer history at entry having rates some 25 to 30 per cent. lower than those seen more promptly.

TABLE II  
RECURRENCE RATES ACCORDING TO LENGTH OF HISTORY AT ENTRY INTO SUPERVISION BY SEX

Sex	Boys		Girls	
	Within 1 Year of Onset	1 Year or More after Onset	Within 1 Year of Onset	1 Year or More after Onset
Number of Children with Recurrences	46	25	68	22
Number of Recurrences	61	32	107	28
Person-Years Observation	480.0	233.0	691.0	299.0
Recurrence Rate	Persons	9.6	Persons	9.8
	Attacks	12.7	Attacks	15.5

The calculated proportion of children who experience recurrent attacks varies, of course, according to the criteria adopted. For instance, in the present series, if a history of recurrent attacks before

observation were accepted, then the overall proportion would become 42 per cent. Limiting consideration to those observed from onset to the time they left school, the figure was 47 per cent. (Table VIII); and for the segment of this group under continuous observation for 3 years or more, the proportion was 54 per cent., a figure which compares with 60 to 75 per cent. given by Hansen (1946) for a similar observation period.

Table III shows recurrence rates according to the manifestation of rheumatism at the onset of the disease. In both sexes, those with carditis alone had a low risk of subsequent recurrence. The group included a number of children who had entered observation with established heart disease of "silent" onset. For other manifestations in the case of boys, rates of recurrence were relatively uniform, but for girls, arthritis and arthralgia carried lower recurrence rates than chorea.

(2) **Nature of Recurrent Attack.**—In Table IV, the type of recurrent attack is related to the nature of the rheumatic manifestation at onset. Where the disease started with chorea, there was a particular likelihood that subsequent episodes would also take the form of chorea, a tendency towards a uniform rheumatic response which was less marked when arthralgia and arthritis had been the mode of onset.

(3) **Annual Risk of a First Recurrent Attack.**—Table V (overleaf) shows the annual risk of a first recurrent episode of acute rheumatism according to length of history from onset, by the conventional life-table technique. This analysis is limited to children who entered observation within one year of developing the disease. It is seen that the risk increased somewhat after the first year, remained almost uniform during the second, third and fourth years, and afterwards diminished only slightly,

TABLE III  
RECURRENCE RATES ACCORDING TO NATURE OF RHEUMATISM AT ONSET, BY SEX

Initial Manifestation	Boys			Girls		
	Observation- Years	Recurrence Rate		Years	Recurrence Rate	
		Persons	Attacks		Persons	Attacks
Carditis Only (Acute or Chronic) .. .. .	66.5	3.0	4.5	48.0	4.2	8.3
Arthritis, Arthralgia, "Limb Pains", with or without Carditis .. .. .	433.5	10.6	13.8	528.5	7.0	9.1
Chorea, with or without Carditis .. .. .	114.0	10.5	15.8	294.5	13.2	22.1
Arthritis or Arthralgia and Chorea, with or without Carditis .. .. .	22.5	13.3	13.3	64.5	14.0	20.2
Other .. .. .	76.5	10.5	11.8	54.5	5.5	9.2
Total .. .. .	713.0	10.0	13.0	990.0	9.1	13.6

TABLE IV  
NATURE OF RECURRENT EPISODES ACCORDING TO NATURE OF ONSET

Onset	No. of Children with Recurrent Episodes	No. of Recurrent Episodes	Recurrent Episodes: No. of Episodes of:							
			Carditis Only		Arthralgia with or without Carditis		Chorea with or without Carditis		Arthralgia and Chorea with or without Carditis	
			No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Carditis Only (Acute or Established) .. .. .	4	7			7	100				
Arthritis, Arthralgia, "Limb Pains", with or without Carditis .. .. .	83	108	17	16	59	55	28	26	4	3
Chorea, with or without Carditis .. .. .	51	83	9	11	12	14	61	74	1	1
Arthritis, Arthralgia, and Chorea, with or without Carditis .. .. .	12	16	1	6	4	25	9	56	2	13
Other (all with Carditis) .. .. .	11	14	5	36	8	57	1	7		
Total .. .. .	161	228	32	14	90	40	99	43	7	3

remaining substantial even in the seventh year after onset.

TABLE V

RISK OF A FIRST RECURRENT ATTACK OF ACUTE RHEUMATISM BY DURATION OF HISTORY (BASED ON THE EXPERIENCE OF CHILDREN\* ENTERING SUPERVISION WITHIN ONE YEAR OF ONSET)

No. of Years after Onset	Persons		Percentage Risk of First Recurrent Attack
	Exposed to Risk	With First Recurrent Attack	
0-	254.0	25	9.8
1-	204.0	31	15.2
2-	147.5	22	14.9
3-	107.0	18	16.8
4-	71.5	9	12.6
5-	48.0	5	10.4
6-	28.0	3	10.7
7-	14.5	—	—
8-	9.0	1	11.1
9+	8.0	—	—

\* The three instances of a first recurrent attack before supervision in this group are not included

It might be argued that the data may be biased because a considerable proportion of children lapsed from observation before reaching school-leaving age. However, an analysis confined to those who were observed from onset up to the time they left school (Table VI) shows an almost identical experience for this segment of patients taken separately. It seems unlikely, therefore, that selective factors seriously impaired the validity of this finding.

TABLE VI

RISK OF A FIRST RECURRENT ATTACK OF ACUTE RHEUMATISM BY DURATION OF HISTORY (BASED ON THE EXPERIENCE OF CHILDREN ENTERING SUPERVISION WITHIN ONE YEAR OF ONSET AND FOLLOWED UNTIL SCHOOL-LEAVING AGE)

No. of Years after Onset	Persons		Percentage Risk of First Recurrent Attack
	Exposed to Risk	With First Recurrent Attack	
0-	178.5	16	9.0
1-	150.5	27	17.9
2-	110.5	16	14.5
3-	82.5	13	15.8
4-	58.0	7	12.1
5-	39.0	4	10.3
6-	24.0	1	4.2
7-	14.5	—	—
8-	9.0	1	11.1
9+	8.0	—	—

Three other analyses (not shown) were also made:

(i) The annual risk of a *second* recurrent attack following the *first*, showed a precisely similar pattern.

(ii) Dividing the patients into two age groups

at the onset of illness—under 10 years, and 10 years of age and over—there was no material difference either in the extent of the annual risk or in the general pattern of the experience.

(iii) Considering separately those patients whose rheumatism first manifested with chorea, the annual risk of a first recurrent attack was somewhat higher than for other rheumatic children, but again it remained relatively uniform after the first year.

Surveys in the United States have differed on the risk of a recurrence according to length of history. For instance, Wilson and Lubschez (1944) and Stollerman (1954) show a considerably greater risk in the first 2 or 3 years after an acute episode than subsequently. The work of Bland and Jones (1951), on the other hand, suggests a high risk for a longer period. However, most surveys have shown that recurrence rates are not negligible even after substantial periods of freedom from active rheumatism, and Mortimer and Rammelkamp (1956), after reviewing the literature, conclude that "... it is mandatory to continue prophylaxis as long as the patient is in school or serving in the armed forces".

(4) **Risk of a Recurrent Episode according to Age.**—Table VII shows recurrence rates (attacks) for each single year of life, based on the experience of all children attending the clinic at these particular ages, who had been first seen within one year of onset. The findings are consistent with the view of a relatively low risk of recurrence up to age 7, and of a substantially greater risk which remained uniform from age 7 to age 15.

TABLE VII

RECURRENCE RATES (ATTACKS) IN SINGLE YEARS OF LIFE, BASED ON CHILDREN ENTERING SUPERVISION WITHIN ONE YEAR OF ONSET

Age (yrs)	Person-Years Observation	Recurrence Rates (Attacks)
3-	8.0	—
4-	18.0	—
5-	33.5	6.0
6-	60.0	5.0
7-	93.5	15.0
8-	119.0	16.0
9-	142.5	18.2
10-	164.5	17.0
11-	187.0	12.3
12-	163.0	14.7
13-	105.0	20.0
14-	45.0	15.6
15-	17.5	11.4
16+	8.5	—

It is seen that recurrence rates were low at ages under 7, and that rates at age 7 to age 15 were in general about three times as high and had no consistent trend within the age range. Experience

at age 15 and over was too small to form the basis of reliable rates.

More detailed analysis (not reproduced here) showed that there was no consistent relationship between age at onset and the recurrence rate at any subsequent age. For instance, children whose rheumatism started at age 6, had a recurrence rate during their thirteenth year of life similar to that of children whose rheumatism had started at age 12. There was no indication either that rheumatism tends "to burn itself out", or that rheumatism starting at a very early age has a greater tendency to recur.

(5) **Significance of Recurrent Episodes in relation to Cardiac Damage.**—It must be recalled that the present series of patients was assembled on the criterion that each had shown unequivocal evidence of cardiac damage at some time during supervision.

88 per cent. of the patients showed signs either of acute carditis or of established heart disease at the time of entry into supervision. By the time supervision had ended, in some patients the clinical signs of cardiac damage had become equivocal or had disappeared altogether. It is a surprising fact that, when the whole series is divided into two groups (those who had experienced recurrent episodes and those who had not), the proportion in whom signs of cardiac damage remained is precisely the same for each—77 per cent.

Probably, however, selective factors have combined to conceal a difference. For instance, the

group with no recurrences included a larger proportion of children who had been supervised at the clinic for a relatively short period, and the average observation period was substantially shorter.

A more accurate picture of the relation between recurrences and permanent cardiac damage is probably afforded by the figures set out in Table VIII, confined to those patients supervised from the onset of the disease until they had left school, although on relatively small numbers the difference shown is barely significant at the customary level.

It is seen that signs of cardiac abnormality remained in 74 per cent. of those who had experienced recurrences, compared with only 61 per cent. of those who had not.

TABLE VIII

CARDIAC ABNORMALITY AT THE END OF SUPERVISION IN RELATION TO RECURRENT ATTACKS BASED ON CHILDREN OBSERVED FROM WITHIN ONE YEAR OF ONSET UNTIL SCHOOL-LEAVING AGE

Recurrent Attacks	Cardiac Abnormality		Normal or No Unequivocal Sign of Cardiac Disease	
	No.	Per cent.	No.	Per cent.
None	59	60.8	38	39.2
One or More	64	74.4	22	25.6

(6) **Trend in Recurrent Attacks, 1931-50.**—Table IX shows annual recurrence rates for each year of

TABLE IX

ANNUAL RECURRENCE RATES AND AVERAGE ANNUAL RECURRENCE RATES FOR QUINQUENNIA 1931-50

Calendar Year	Person-Years Observation	Recurrence Rates			
		Persons		Attacks	
		Annual	Average for Quinquennium	Annual	Average for Quinquennium
1931	42.0	9.5	15.7	9.5	17.6
32	71.0	21.1		26.8	
33	100.5	13.9		14.9	
34	121.5	21.4		23.0	
35	137.5	12.4		13.8	
1936	135.0	17.7	14.2	17.7	14.2
37	139.5	10.8		10.8	
38	120.0	12.5		12.5	
39	100.5	16.9		16.9	
40	82.5	13.3		13.3	
1941	70.5	8.5	10.6	8.5	10.9
42	63.5	12.6		12.6	
43	60.0	10.0		11.7	
44	59.5	11.8		11.8	
45	60.5	9.9		9.9	
1946	60.0	13.3	11.2	15.0	11.9
47	57.0	12.3		12.3	
48	60.0	13.3		13.3	
49	58.0	6.9		8.6	
50	58.0	10.2		10.3	



the period, together with average rates for quinquennia. There was an apparent decline in frequency over the years, the average annual rates for 1946-50 being some 30 per cent. below those for the first quinquennium. Most of the decline took place between 1936-40, and 1941-45, the average rates for the latter quinquennium, indeed, being the lowest of all.

The present data does not, however, furnish conclusive evidence of a *true* decline. In the earlier years, patients more frequently lapsed from supervision and the possible effect of this on the calculated rates, and on the trend, is problematical. Moreover, as Wilson and Lubschez (1944) have suggested, a change in the type of case coming under supervision may influence the annual recurrence rate, though there was no evidence in the present series that such a change had occurred.

If, however, the observed rates do reflect a real trend in frequency, then it may be asked whether the fall was related to changing circumstances as the years went by, or whether the period in which acute rheumatism first developed determined the subsequent risk of a recurrent episode.

Table X analyses recurrence rates in quinquennia according to period of onset. The figures relate only to those patients for whom a precise date on onset was recorded. In no single quinquennium was there any substantial tendency for the patients with earlier onset to experience higher rates of recurrence. If the trend were a real one, then Table X would suggest that recurrence rates were influenced by changing conditions and not deter-

mined by the circumstances attending the onset of the disease.

It is noteworthy that the observed decline was much less marked than the fall in inception rates of acute rheumatism in Cardiff school-children (Hitchens, 1956). Over the same period, the inception rate was reduced to one-third.

(7) **Seasonal Occurrence.**—There seems no obvious *a priori* reason why the seasonal frequency of recurrent episodes of rheumatism should differ from that characterizing the onset of the disease. Yet, in the present series, a difference was found. The figures are set out in Table XI (opposite). Again, the analysis was necessarily confined to children for whom the relevant information was available.

Statistically, there is a significant difference between the monthly distribution of onset and that of recurrence in children with heart disease. Recurrent episodes were most frequent in January, March, and November; rather more than 40 per cent. of the recurrences were experienced in the first quarter of the year, and only 28 per cent. in the fourth quarter. By contrast, for initial attacks, October and December were worse months than January; 36 per cent. of cases had an onset in the fourth quarter of the year, compared with only 23 per cent. in the first quarter.

It is always difficult to assess the epidemiological significance (if any) of seasonal irregularities of this kind, and no explanation can be offered for the differences found. It may be pointed out, however, that a similar analysis of the second group of rheumatic cases attending the Cardiff clinic (those

TABLE X  
RECURRENCE RATES IN QUINQUENNIA ACCORDING TO PERIOD OF ONSET OF DISEASE, BASED ON PATIENTS WITH A KNOWN DATE OF ONSET

Period of Onset	Quinquennium of Recurrences							
	1931-5		1936-40		1941-5		1946-50	
	Recurrence Rate		Recurrence Rate		Recurrence Rate		Recurrence Rate	
	Persons	Attacks	Persons	Attacks	Persons	Attacks	Persons	Attacks
Before 1931	17.9 (28)	19.4 (30)	16.0 (6)	16.0 (6)				
1931-35	16.3 (43)	18.3 (48)	14.7 (50)	14.7 (50)	6.3 (3)	6.3 (3)	0.0 (0)	0.0 (0)
1936-40			15.7 (21)	15.7 (21)	12.0 (19)	12.0 (19)	2.6 (1)	2.6 (1)
1941-45					10.0 (9)	11.1 (10)	12.8 (20)	13.5 (21)
1946-50							14.6 (12)	15.9 (13)

Figures in parentheses are the number of patients and recurrent episodes on which the rates are based.

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TABLE XI

SEASONAL DISTRIBUTION OF MONTH OF ONSET AND OF RECURRENT ATTACKS, BASED ON ALL PATIENTS FOR WHOM DATES WERE PRECISELY RECORDED\*

Type of Case	Month of Onset												Month of Recurrence											
	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
<i>With Carditis:</i>																								
Number ..	29	16	19	24	20	17	13	14	19	38	23	40	41	19	28	12	10	21	13	10	16	17	25	21
Number Corrected to 31-day Month..	29	18	19	25	20	18	13	14	20	38	24	40	41	21	28	12	10	22	13	10	16	17	26	21
Per cent. Average Monthly Number ..	125	78	82	108	86	78	56	60	86	164	103	172	208	106	142	61	51	111	66	51	81	86	132	106
<i>Without Evidence of Carditis:</i>																								
Number ..	40	31	24	27	24	25	20	22	27	34	20	46	33	22	29	20	11	15	17	18	20	13	19	20
Number Corrected to 31-day Month..	40	34	24	28	24	26	20	22	28	34	21	46	33	24	29	21	11	15	17	18	21	13	20	20
Per cent. Average Monthly Number ..	138	118	83	97	83	90	69	76	97	118	73	159	163	119	144	104	54	74	84	89	104	64	98	98

\* The monthly distributions of onset and of recurrence for patients with carditis differ significantly.  $\chi^2=24.35$ ;  $n^1=11$ ;  $0.02 > p > 0.01$ . January, March, October, and December together account for two-thirds of the value of  $\chi^2$ . The distributions for patients without carditis are not significantly different.  $\chi^2=14.92$ ;  $n^1=11$ ;  $0.20 > p > 0.10$ .

without heart disease), which is also shown in Table XI, has some points of similarity. Again, recurrences were heavy in the first quarter of the year (36 per cent.) and relatively infrequent in the fourth quarter (22 per cent.), and the episodes were most numerous in January. Corresponding figures for onset in this group were 28 per cent. in the first quarter and 29 per cent. in the fourth quarter, December being the month of highest incidence.

(8) *Relation with Social Status.*—Here, in particular, there may be some bias, arising perhaps from a higher degree of ascertainment among the less well-to-do. Table XII does, however, suggest that

children living in the least favourable physical environment may have been subject to the greatest risk of recurrence.

In the absence of a more precise index, children were divided according to school of attendance (excluding grammar schools and special schools), classified subjectively on a four-point social scale. Those attending older working-class type schools had rates somewhat in excess of the other groups; there is also a social gradient for recurrence rates (attacks), though not a substantial one for recurrence rates (persons).

## Comment

The main interest of the present findings centres in the risk of a recurrent episode according to length of history and age. During the period considered, specific prophylaxis was not a routine procedure, and the figures consequently represent the "natural" tendency of acute rheumatism to recur in this particular clinic population. The results are approximately comparable with those of two of the American surveys mentioned earlier: one by Wilson and Lubschez (1944) and the other by Bland and Jones (1951). In the first of these, based on 3,957 patient-years experience, there was a high recurrence rate from age 4 to age 13, rates about half to one-third lower from age 14 to age 16, and still lower rates thereafter. The risk of a recurrence was greatest in

TABLE XII  
RECURRENCE RATES ACCORDING TO TYPE OF SCHOOL ATTENDED

Type of School Serving:	Person-Years Observation	Recurrence Rate	
		Persons	Attacks
(1) Old Working-Class Area ..	772.0	11.3	16.1
(2) New Council Estate	283.0	8.7	13.1
(3) Mixed Working and Middle-Class Area	443.0	7.7	11.8
(4) Mainly Middle-Class Area ..	131.0	7.6	8.4

the first year after an acute episode, lower in the second year, and subsequently lower thereafter. The second American survey showed that recurrent episodes occurred annually in one patient in five for the first 5 years after onset, in one in ten for the second 5 years, in one in twenty for the third 5 years, and thereafter much less frequently.

As regards age, the present findings differ only slightly from those of Wilson and Lubschez in that rates were relatively low up to age 7, and that there was no marked decline from age 13 to age 15. They agree in showing a high sustained rate from age 7 to age 13. As regards risk of recurrent attack according to length of history, the results would seem to agree more closely with the second survey. The chance of a first recurrent attack remained substantial even in the seventh year after onset.

Recently, both the Royal College of Physicians of London (1957) and the American Heart Association (1957) have reiterated that, if specific prophylaxis is contemplated, it should be continued throughout the years of childhood after an attack of rheumatic fever. Retrospectively, the experience of the Cardiff Clinic in the 20 years from 1931-50 shows that no less rigorous a preventive programme would have been fully effective. Furthermore, the seasonal trend in the frequency of recurrent attacks, although quite marked, would not have justified omitting prophylaxis during the summer months.

### Summary

The experience of recurrent attacks of acute rheumatism in a group of Cardiff children with rheumatic heart disease, who attended the School Rheumatism Clinic from 1931-50, is described. The main findings were as follows:

- (1) Recurrent episodes were observed in about one-third of the whole group; in 47 per cent. of those under supervision from onset to school-leaving age; and in 54 per cent. of those who were observed continuously for 3 years or more after onset. In girls, recurrences were most frequent when the illness started with chorea.
- (2) When chorea was an initial manifestation, there was a particular likelihood that chorea would also be a feature of recurrent attacks.
- (3) The risk of a first recurrent attack of rheumatism remained substantial even in the seventh year after onset. The risk diminished only slightly after the first 4 years.

- (4) Recurrence rates were relatively low up to age 7, but remained at a high level from age 7 to age 15.
- (5) Among children observed from onset to the time of leaving school, cardiac abnormality remained at the end of the supervision period in 74 per cent. of those who experienced recurrences and in 61 per cent. of those who did not.
- (6) There was an apparent decline in the frequency of recurrent attacks over the 20-year period.
- (7) There was a marked seasonal trend in frequency, but the number of recurrent attacks in the summer months was not negligible. The seasonal pattern of recurrent episodes differed from that of initial attacks in a manner which could not be explained.
- (8) There was some suggestion of a social gradient in recurrence rates.

The implication of some of these findings in relation to prophylaxis is mentioned.

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### Rechutes du rhumatisme articulaire aigu chez des écoliers

#### RÉSUMÉ

On a étudié les rechutes du rhumatisme articulaire aigu chez un groupe d'enfants de Cardiff atteints de la maladie de Bouillaud et observés à la Clinique Rhumatologique Scolaire entre 1931 et 1950. Voici les résultats principaux:

- (1) Des rechutes ont été observées dans à peu près un tiers du groupe entier; chez 47% de ceux suivis dès le début de la maladie jusqu'à la fin de l'âge scolaire; et chez 54% de ceux suivis pendant 3 ans après le début. Chez les filles, les rechutes étaient plus fréquentes lorsque la maladie avait commencé par la chorée.



(2) La chorée de la première attaque tendait à se reproduire au cours des rechutes.

(3) La probabilité de la première rechute ne diminuait que faiblement quatre ans après la première attaque et demeure assez importante après sept ans.

(4) La proportion des rechutes est relativement basse jusqu'à l'âge de 7 ans et augmente considérablement entre 7 et 15 ans.

(5) Parmi les enfants suivis dès le début de la maladie jusqu'au moment de quitter l'école, la lésion cardiaque fut retrouvée à la fin de la période d'observation chez 74% de ceux qui eurent des rechutes et chez 61% de ceux qui n'en eurent pas.

(6) Il y avait une diminution apparente de la fréquence des rechutes sur une période de 20 ans.

(7) La fréquence des rechutes tendait à varier fortement selon la saison, mais le nombre d'attaques en été n'était pas négligeable. Le type saisonnier des rechutes différait de celui des attaques initiales d'une manière inexplicable.

(8) Le facteur social semblait jouer un rôle dans la fréquence des rechutes.

On fait mention des implications de quelques de ces résultats dans la question de prophylaxie.

# Accesos recurrentes del reumatismo poliarticular agudo en niños de escuela

## SUMARIO

Se estudiaron los accesos recurrentes del reumatismo poliarticular agudo con lesión cardíaca en un grupo de niños de Cardiff observados en la Clínica Reumatológica

Escolar entre los años de 1931 y 1950. Los resultados principales fueron los siguientes:

(1) Accesos recurrentes fueron observados en cerca de una tercera parte del grupo entero; en un 47% de los niños observados desde el comienzo de la enfermedad hasta el cumplir la edad escolar; y en un 57% de los observados durante 3 años al menos desde el comienzo. En las muchachas, las recaídas fueron más frecuentes cuando la enfermedad había empezado por la corea.

(2) La corea del acceso inicial tendía a manifestarse en las recaídas.

(3) La probabilidad de la primera recaída baja un poco cuatro años después del primer acceso, pero aún queda bastante importante siete años después.

(4) La proporción de las recaídas es relativamente baja hasta la edad de 7 años, pero sube considerablemente entre los 7 y los 15 años.

(5) Entre los niños observados desde el comienzo de la enfermedad hasta el fin de la edad escolar, la lesión cardíaca fué encontrada al cabo del período de observación en un 74% de los que manifestaron recaídas y en un 61% de los que no los tuvieron.

(6) Hubo una baja aparente de la frecuencia de las recaídas en un período de 20 años.

(7) La frecuencia de las recaídas tendía a variar fuertemente según el tiempo del año, pero el número de accesos en verano no fué despreciable. El tipo tempestivo de las recaídas difería del de los accesos iniciales de una manera inexplicable.

(8) El factor social pareció desempeñar un papel en la frecuencia de los accesos recurrentes.

Se mencionan las implicaciones de algunos de estos resultados respecto a la profilaxis.

## APPENDIX

It has been stated in the text that a substantial proportion of children were lost to supervision for one reason or another before leaving school. Among 272 children seen within one year of onset, 68 per cent. were followed until the time they left school, 8 per cent. were still attending the clinic when the inquiry ended, and 24 per cent. lapsed. Among the remainder who entered supervision at a later stage of their illness, the corresponding figures were 36, 2, and 62 per cent.—i.e. there was a much higher lapse rate. The mean observation periods for the two groups were 4.3 and 2.7 years respectively.

The distribution of all children entering supervision during the 20 years by duration of observation period was as shown in the Table.

The method of computing person-years observation was the usual one, based on the assumption that entries and withdrawals were uniformly distributed over the year. For instance, in relation to

Years	No. of Children	Years	No. of Children
0 (no supervision)	6	5—	41
0—	91	6—	40
1—	65	7—	20
2—	58	8—	15
3—	61	9—	10
4—	54	10+	9

total observation period, the number of completed years of supervision for each patient had been coded, and to these on each withdrawal was added a further 6 months' exposure to risk. For computing person-years observation in calendar years, 6 months' exposure to risk was allowed both in the year of entry and in the year of withdrawal. The numerical differences as between one context and another do not exceed 5 per cent. That they were as great as this probably means that the assumption for this group of patients was only approximately true. There is also a further source of discrepancy: when rates relate to total observation period, a child



who experienced two recurrent attacks appears only once in the Recurrence Rate (Persons); when rates relate to calendar years, however, he may appear in the rate for each of the years when the recurrent attack took place.

The six children seen on one occasion only have been allowed no experience throughout the investigation.

Throughout the paper, differences have been considered significant at the 5 per cent. level.

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RHEUMATOID ARTHRITIS OF THE CERVICAL SPINE IN THE ADULT

BY

J. SHARP, D. W. PURSER, AND J. S. LAWRENCE

From the Departments of Rheumatism Research and Orthopaedic Surgery and the Empire Rheumatism Council Field Unit, University of Manchester

Garrod (1890), who first differentiated rheumatoid arthritis as a clinical entity, noted that the cervical spine was affected in 178 of his 500 patients. Sharp (1957) found that the cervical spine was affected clinically at some stage of the disease in 40 per cent. of the patients attending the Manchester Rheumatism Centre with rheumatoid arthritis; almost all of these were adults and in some cases the cervical involvement was a major source of disability. Involvement of the cervical spine is generally recognized as a common feature of juvenile rheumatoid arthritis (Still, 1897; Coss and Boots, 1946; Potter, Barkin, and Stillman, 1954; Ziff, Contreras, and McEwen, 1956), but little attention has been paid to the changes produced in this region in the adult form of the disease.

The purpose of the present study was to define the radiological changes produced in the cervical spine by rheumatoid arthritis in the adult and to discover whether such changes may occur as the only evidence of rheumatoid arthritis, that is without clinical or radiological signs of the disease elsewhere. We subscribe to the view held by most British and many American authors that rheumatoid arthritis and ankylosing spondylitis are distinct diseases (Golding, 1935; Dunham and Kautz, 1941; Buckley, 1945; Hart, Robinson, Allchin, and MacLagan, 1949; Mowbray, Latner, and Middlemiss, 1949; Ziff, Brown, Badin, and McEwen, 1954). This report is concerned only with cervical involvement in rheumatoid arthritis as such.

Material and Methods

During the years 1953-5 inclusive, in-patients in the Rheumatism Centre of the Manchester Royal Infirmary had a routine series of radiographs including a lateral view of the cervical spine. Only those of patients between the ages of 55 and 64 years were used for this study (16 were males and 28 females). These were compared with films of 15 males and 28 females in this age group taken from the general population of Leigh,

Lancashire. These were selected at random from the series studied by Kellgren and Lawrence (1956).

The films were read by the three authors in consultation and all the abnormalities observed were tabulated. Scores of from 0 to 4 were used to indicate the severity of each abnormal feature:

- 0=absent
- 1=doubtful
- 2=minimal
- 3=moderate
- 4=severe

The sample of films from the general population was found to contain a proportion from individuals with rheumatoid arthritis. The subsequent analysis was, therefore, made first on the total sample, then with the rheumatoid subjects excluded.

Some features of the rheumatoid patients are indicated in Table I. All patients were classified according to the diagnostic criteria for rheumatoid arthritis proposed by

TABLE I  
DATA ON RHEUMATOID PATIENTS SELECTED FOR THIS STUDY

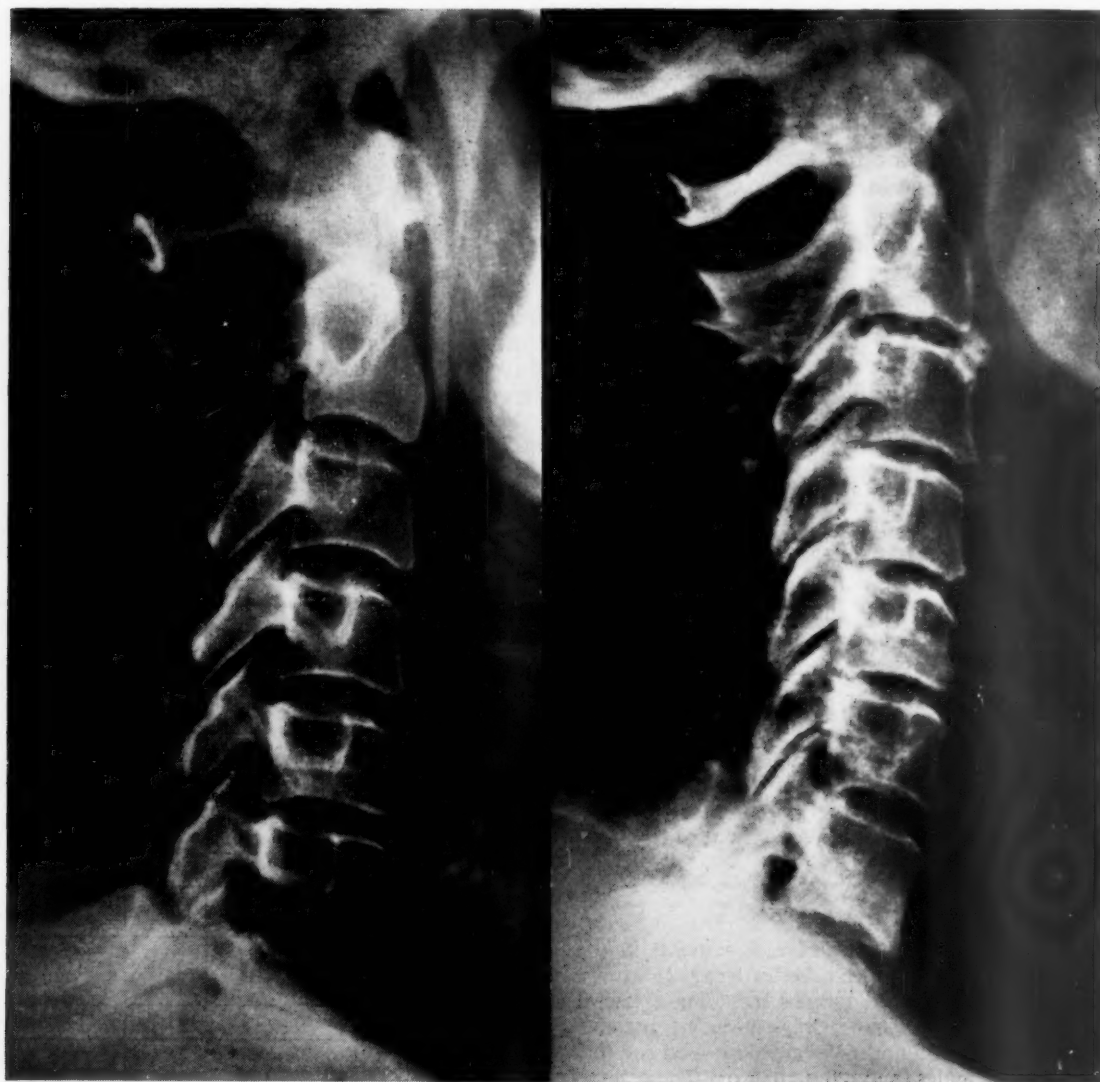
Sex	Male	Female	Total	
Total Number of Patients	16	28	44	
American Rheumatism Association Classification	Definite	15	28	43
	Probable	1	0	0
Duration of Symptoms (yrs)	Average	4.3	9.3	7.5
	Range	4/12-16	1-36	4/12-36
Subcutaneous Nodules Present	6	11	17	
Erythrocyte Sedimentation Rate (Westergren) (mm./hr)	Average	67	59	62
	Range	22-140	23-119	22-140
Sheep Cell Agglutination Test	Total Tested	15	26	41
	No. Positive (at least one reading of 1/32 or higher titre)	14	24	38

the American Rheumatism Association (Ropes, Bennett, Cobb, Jacob, and Jessar, 1956). All except one fell into the definite category. All had a raised erythrocyte sedimentation rate and the majority were suffering from very active disease, probably of more than average severity, in view of the selection factors operative in bringing patients to a special centre. The sheep cell agglutination test was performed by the method of Ball (1950), and we are grateful to Dr. Ball for carrying out the tests used in this study. The result was positive in 92 per cent. of the patients tested.

Comparison of the abnormal features in the two series of films revealed that certain abnormalities were commoner in the rheumatoid patients. Using these features as criteria, 428 cervical radiographs, taken from random

samples of the populations of Leigh and of Cowbridge, in the Vale of Glamorgan, in the age group 55-64 years were read independently by the three observers in an effort to recognize the subjects suffering from rheumatoid arthritis from the radiographic appearances of the cervical spine alone. The films were therefore read without knowledge of the clinical or serological findings, or of the radiological findings elsewhere. Each film was awarded a grading for rheumatoid arthritis of from 0 to 4 as previously defined. Films from the original series of rheumatoid patients, representative of Grades 2, 3 and 4 were selected for use as standards; these are illustrated in Fig. 1.

From the readings of these three observers it was possible to assess interobserver error. For the assess-



Grade 0

Grade 2

Fig. 1.—Standard films used in grading rheumatoid changes.

ment of intra-observer error, a group of 100 films, which included those of all subjects in the population sample with a positive sheep cell test (except one), was re-read independently by one of the observers some months after the original reading and again a third time a week after the second reading.

### Results

#### Readings on Known Rheumatoid and Non-Rheumatoid Subjects

The main differences between the prevalence of abnormal features in the films of the rheumatoid patients and those in films of the general population are set out in Table II (overleaf). Rheumatoid arthritis of the cervical spine was characterized by

changes in the intervertebral disks, vertebral plates, and apophyseal joints, and by vertebral subluxation.

In the rheumatoid patients, narrowing of disk spaces, where present, tended to affect multiple levels. The disks between the second and third and between the third and fourth vertebrae, which were rarely affected in the non-rheumatoid subjects, were quite frequently involved in those with rheumatoid arthritis. Below C4, disk narrowing was common in both groups, rather more so in those without rheumatoid arthritis. Disk narrowing with little or no osteophytosis was a feature of rheumatoid spines, but marked osteophytosis with severe sclerosis of the vertebral plates was more frequent in the non-rheumatoid subjects. In the rheumatoid pat-



Grade 3

Grade 4

Fig. 1.—Standard films used in grading rheumatoid changes.



TABLE II

COMPARISON OF RADIOLOGICAL CHANGES IN THE CERVICAL SPINE IN RHEUMATOID HOSPITAL IN-PATIENTS AND CONTROLS FROM A RANDOM SAMPLE OF THE GENERAL POPULATION, BOTH AGED 55-64 YRS

Characteristics Examined			Rheumatoid Hospital In-Patients	Random General Population Sample		Rheumatoid Hospital In-Patients	Random General Population Sample (Definite Non-R.A.*)	P of Difference R.A./Non-R.A. as Proportion of	
				Total	Definite Non-R.A.*			Total	Those with Narrow Disks
			Numbers			Per cent. of Total			
Disk Narrowing	Number of Disks Affected	None ..	13	7	6	30	17		
		One ..	7	13	12	16	34		
		Two ..	10	11	9	22	26		
		Three or More ..	14	12	8	32	23		
	Levels Affected	C.2/3 ..	4	1	0	9	0	< .05	< .01
		C.3/4 ..	9	5	3	20	9		
		C.4/5 ..	15	15	12	34	34		
		C.5/6 ..	26	29	23	59	66		
C.6/7 ..		18	25	20	41	57			
Accompanying Osteo- phytosis	Little or None ..	11	4	3	25	9	< .11	< .05	
	Marked ..	20	32	26	45	74			
Affection of Vertebral Plates	Sclerosis	Minimal ..	10	9	6	22	17	~ .10	~ .19
		Moderate to Severe ..	6	13	11	14	31		
	Erosion	Minimal to Severe ..	9	6	3	20	9	~ .25	< .14
Vertebral Subluxation	Total ..	..	12	6	6	27	17	~ .4	< .01
	Mild ..	..	4	6	6	9	17		
	Moderate ..	..	7	0	0	16	0		
	Severe ..	..	1	0	0	2	0	< .02	
	At Multiple Levels ..	..	4	1	1	9	3		
Apophyseal Joint Changes	Prolif- erative	Total Definite ..	15	14	13	34	37		
		At Multiple Levels ..	8	11	11	18	31		
	Destruc- tive	Total Definite ..	10	2	2	23	6	< .08	
		At Multiple Levels ..	8	0	0	18	0	< .02	
Total Number of Films ..			44	43	35	100	100		

\* i.e. after excluding individuals who showed any of the following features: Sheep Cell Agglutination Test Titre of 1/32 or more, Definite Clinical Rheumatoid Arthritis. Definite Radiological Rheumatoid Arthritis of Hands and/or Feet.

ients, however, appearances suggesting erosions of the vertebral plates were more often encountered.

Vertebral subluxation of more than mild degree was observed *only* in the rheumatoid patients. Minor subluxations were found in both rheumatoid and non-rheumatoid subjects at the disk immediately above a degenerate disk or block vertebra. In the rheumatoid patients, subluxation sometimes occurred without obvious cause, often through a grossly narrowed disk. In the one patient with severe subluxation, this occurred at multiple levels, the most severe being an 8 mm. forward displacement of the atlas on the axis.

Erosion of the apophyseal joints was observed more frequently in films of the rheumatoid patients, but in "blind" reading of films changes in the apophyseal joints were difficult to detect with certainty and were not found to be very helpful diagnostically; as the sole evidence of rheumatoid

arthritis they were even occasionally misleading. The greatest reliance in the diagnosis of rheumatoid arthritis was placed on the presence of narrowing of multiple disk spaces, particularly those between the second and third and third and fourth vertebrae, and subluxation of vertebrae of more than mild degree, particularly if multiple or if occurring through an obviously narrowed disk space. Complete or relative absence of osteophytosis or sclerosis of vertebral plates in relation to narrowed disk spaces was also helpful.

#### Readings on Films from Population Samples

**Observer Agreement.**—If the above criteria are to be of value in diagnosis, it must be shown that a good measure of agreement is possible between different observers and between repeated readings of the same observer.

TABLE III

INTEROBSERVER DIFFERENCES IN GRADING RHEUMATOID ARTHRITIS FROM X-RAY READINGS OF THE CERVICAL SPINE

Observer A						Observer A					
	302	94	24	8	428		302	94	24	8	428
3	—	—	1	2	3	3	—	2	2	3	7
2	6	18	14	5	43	2	7	12	11	2	32
1	27	34	7	1	69	1	49	52	7	1	109
0	269	42	2	—	313	0	246	28	4	2	280
Grade	0	1	2	3		Grade	0	1	2	3	

$$r = +0.66$$

$$r = +0.58$$

TABLE IV

INTRA-OBSERVER DIFFERENCES IN GRADING RHEUMATOID ARTHRITIS FROM X-RAY READINGS OF THE CERVICAL SPINE

A1						A2					
	70	24	4	2	100		65	26	5	4	100
3	—	2	—	2	4	3	—	—	—	4	4
2	2	2	1	—	5	2	—	6	4	—	10
1	9	14	3	—	26	1	1	13	1	—	15
0	59	6	—	—	65	0	64	7	—	—	71
Grade	0	1	2	3		Grade	0	1	2	3	

$$r = +0.61$$

$$r = +0.89$$

In Table III Observer A is compared with Observers B and C in readings of the 428 cervical films from the Leigh and Cowbridge surveys. Observer B graded fewer x rays as 3 or 1, and more as 2 or 0 compared with Observer A. Observer C graded more as 1 or 2, and fewer as 0. Nevertheless, the correlation coefficients showed a satisfactory positive correlation, being respectively thirteen times and twelve times the standard error.

In the second readings by Observer A (Table IV), more films were graded 3, 2, and 1, and fewer were graded 0. The correlation coefficient is of the same order as for interobserver comparisons. In the third reading the films graded 3 were identical, but more were graded 2 and 0 and fewer 1. Between the second and third readings there was a very high degree of correlation ( $r = +0.89$ ).

**Prevalence of Radiological Signs of Cervical Rheumatoid Arthritis and Comparison with Other Evidence of Rheumatoid Arthritis.**—The prevalence of definite radiological changes (Grade 2 to 4) of rheumatoid arthritis (Table V, overleaf) in the cervical spine,

using the average reading of three observers, was 6 per cent. in males and 7 per cent. in females. Though the prevalence was thus similar in the sexes, the severity was greater in females, who alone showed Grade 3 to 4 changes. Doubtful changes were also more frequent in females. In both sexes there was a relationship between the severity of the x-ray changes and the proportion having a positive sheep cell agglutination test. For both sexes together (Fig. 2, overleaf), the proportion of positive sheep cell tests varied from 3 per cent. in those with no x-ray changes to 17 per cent. in those with definite rheumatoid arthritis. This association is highly significant ( $P = <0.01$ ).

A clinical diagnosis of rheumatoid arthritis had been made in 41 of the 428 persons in this series (Table VI, overleaf); the prevalence of clinical rheumatoid arthritis varied from 9 per cent. in those with no x-ray changes in the cervical spine to 14 per cent. in those with definite changes. The association, however, could not be regarded as significant ( $P = 0.6$ ). Division of the cases of clinical rheumatoid arthritis into those with and those without a

TABLE V

COMPARISON OF SHEEP CELL AGGLUTINATION TEST WITH CERVICAL X-RAY CHANGES (AVERAGE READINGS OF THREE OBSERVERS)

Sheep Cell Agglutination Test Titre	Grading of Rheumatoid Arthritis												Total No.
	Males (159)				Females (269)				Both Sexes (428)				
	0	1	2	3-4	0	1	2	3-4	0	1	2	3-4	
0	73	14	5	—	131	45	9	1	204	59	14	1	278
1/4	27	14	3	—	28	7	2	—	55	21	5	—	81
1/8	9	2	—	—	14	6	2	—	23	8	2	—	33
1/16	3	—	1	—	6	3	1	—	9	3	2	—	14
1/32	1	1	—	—	2	3	1	1	3	4	1	1	9
1/64	2	—	—	—	2	—	1	—	4	—	1	—	5
1/128	—	—	1	—	—	1	—	1	—	1	1	1	3
1/256	1	1	—	—	1	1	—	—	2	2	—	—	4
1/512	1	—	—	—	—	—	—	—	1	—	—	—	1
Total No. ..	117	32	10	—	184	66	16	3	301	98	26	3	428
Positive SCAT Per cent.	4	6	10		3	8	21		3	7	17		

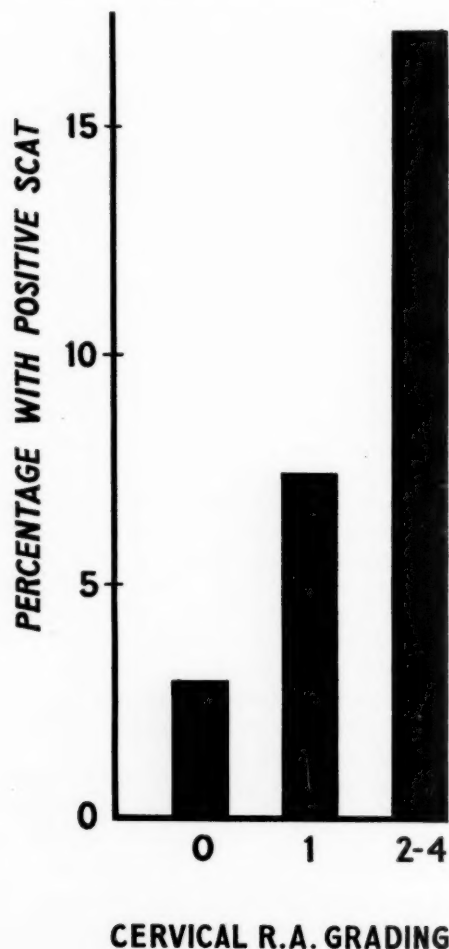


Fig. 2.—Relationship of rheumatoid x-ray changes in the cervical spine to sheep cell agglutination test.

TABLE VI

COMPARISON OF CLINICAL RHEUMATOID ARTHRITIS AND CERVICAL X-RAY CHANGES (AVERAGE OF READINGS OF THREE OBSERVERS)

Clinical R.A. Gradings	Gradings of Cervical Changes				
	Total No.	0	1	2	3-4
0	356	253	78	23	2
1	31	21	10	—	—
2	29	19	9	1	—
3	4	3	1	—	—
4	8	5	0	2	1
Total No. . . . .	428	301	98	26	3
Percentage Grades 2-4 . . . . .	—	9	10	14	—
Morning Stiffness	No. . . . .	123	84	31	7
	Per cent. . . . .	—	28	32	28
Past Polyarthritis Only . . . . .	44	42	2	0	0

positive sheep cell test also failed to disclose any significant association (Table VII, opposite). Morning stiffness similarly showed no association with x-ray changes and none of the patients who had only a history of a previous attack of polyarthritis had x-ray evidence of rheumatoid arthritis in the cervical spine.

The hands and feet of all the 428 persons in this series were x-rayed during the original survey. Radiological evidence of rheumatoid arthritis in one or both of these sites had been discovered in 33 (8 per cent.) (Table VIII; Fig. 3, opposite); x-ray changes were three times as frequent in the hands and feet of those with Grade 2 to 4 changes in the cervical spine as in those with Grade 0 to 1 changes. This association is significant ( $P=0.02$  to  $0.01$ ). The correlation coefficient using all gradings is low

TABLE VII

THE RELATIONSHIP OF CERVICAL RHEUMATOID ARTHRITIS TO CLINICAL RHEUMATOID ARTHRITIS IN PERSONS WITH POSITIVE AND NEGATIVE SHEEP CELL TESTS

Clinical RA Grading		Cervical RA Grading				Total No.
		0	1	2	3	
Positive SCAT	0	6	3	2	1	12
	1	—	1	—	—	1
	2	1	2	—	—	3
	3	—	1	—	—	1
	4	3	—	1	1	5
Total No.		10	7	3	2	22
Negative SCAT	0	247	75	21	1	344
	1	21	9	—	—	30
	2	18	7	1	—	26
	3	3	—	—	—	3
	4	2	—	1	—	3
Total No.		291	91	23	1	406
Per cent. with Clinical RA Grades 2-4 with Negative SCAT		8	8	8		
Grand Total		301	98	26	3	428

TABLE VIII

THE RELATIONSHIP OF X-RAY CHANGES OF RHEUMATOID ARTHRITIS IN THE CERVICAL SPINE AND IN HANDS AND/OR FEET

Radiological R.A. of Hands and/or Feet Grading		Cervical RA Grading				Total No.
		0	1	2	3-4	
Positive SCAT	0	4	4	—	—	8
	1	2	3	—	1	6
	2	1	—	2	—	3
	3	1	—	—	—	1
	4	2	—	1	1	4
Total No.		10	7	3	2	22
Negative SCAT	0	176	50	12	—	238
	1	98	35	9	1	143
	2	15	6	1	—	22
	3	1	—	—	—	1
	4	1	—	1	—	2
Total No.		291	91	23	1	406
Per cent. with Grade 2-4 RA Hands and/or Feet		6	7	8		6
Grand Total		301	98	26	3	428
Per cent. with Grade 2-4 RA Hands and/or Feet		7	6	21		8

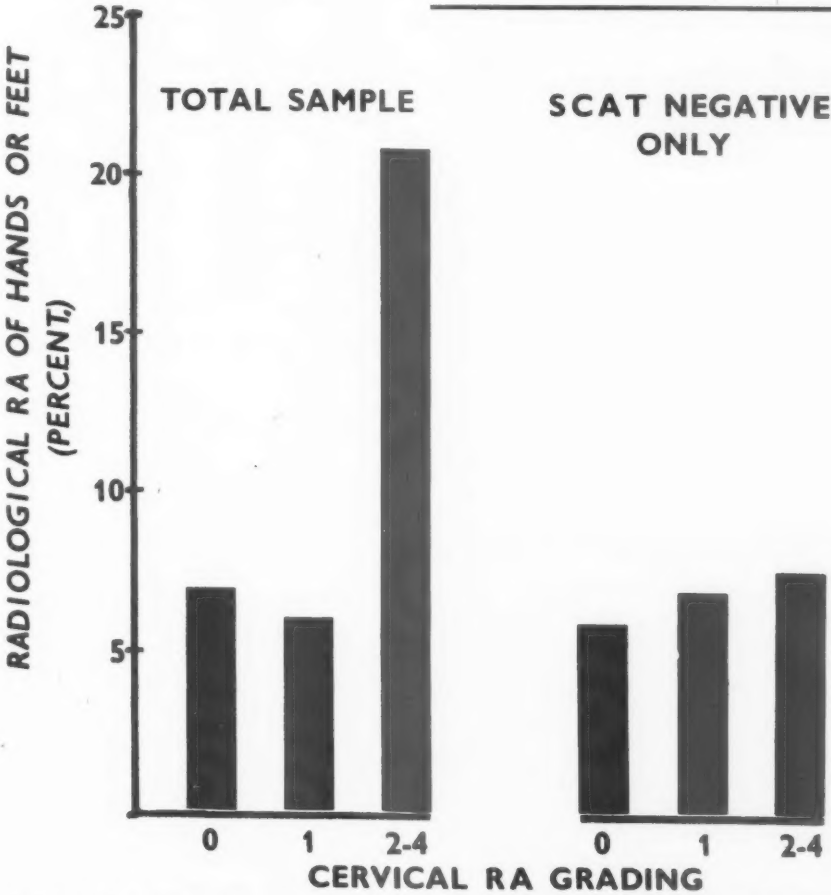


Fig. 3.—Relationship of radiological changes of rheumatoid arthritis in the cervical spine to those in the hands and feet.



( $r=+0.12$ ), but with a standard error of 0.05 is significant. The association was virtually confined to those with positive sheep cell tests.

As a composite assessment of clinical, radiological and serological evidence of rheumatoid arthritis, the American Rheumatism Association's classification (Ropes and others, 1956) has been used (Table IX). In this classification, which is based on a points system, one point is given for radiological evidence of rheumatoid arthritis which must include at least osteoporosis in the region of the affected joint. In applying the A.R.A. classification for the present purposes, radiographic changes in the cervical spine have been excluded. This is in conformity with current clinical practice, since a radiograph of the cervical spine is not normally included in the routine investigation of a patient suspected of having rheumatoid arthritis. Using these criteria, a diagnosis of definite rheumatoid arthritis was made in fourteen (3 per cent.) of the 428 persons in this series. A further 10 per cent. had probable and 14 per cent. possible rheumatoid arthritis. There was only a poor association between the disease as defined in this classification and the changes we have assessed in the cervical spine.

TABLE IX

COMPARISON OF AMERICAN RHEUMATISM ASSOCIATION CLASSIFICATION WITH CERVICAL X-RAY CHANGES

A.R.A. Classification	Grading of Cervical Changes				
	Total No.	0	1	2	3-4
Definite .. ..	14	9	3	1	1
Probable .. ..	44	30	12	2	—
Possible .. ..	60	39	15	5	1
None .. ..	307	220	68	18	1
Not Stated .. ..	3	3	—	—	—
Total No. .. ..	428	301	98	28	3
Possible—Definite as Per cent. .. ..		26	31	34	

It is thus apparent that, in the type of case predominating in these population samples, both the sheep cell test and radiological changes in the hands and feet correlated to a significant degree with the cervical changes. Clinical rheumatoid arthritis on the other hand showed no close association. There was, however, a definite correlation ( $P<0.01$ ) between clinical rheumatoid arthritis and the sheep cell test (Table X) and between the sheep cell test and radiological evidence of rheumatoid arthritis in the hands and feet ( $P<0.01$ , Table XI).

TABLE X  
COMPARISON OF CLINICAL RHEUMATOID ARTHRITIS WITH SHEEP CELL AGGLUTINATION TEST

SCAT Titre	Total No.	Grading of Clinical R.A.				
		0	1	2	3	4
0	278	238	19	17	1	3
1/4	81	68	4	7	2	—
1/8	33	26	6	1	—	—
1/16	14	12	1	1	—	—
1/32	9	6	1	2	—	—
1/64	5	4	—	—	—	1
1/128	3	1	—	—	—	2
1/256	4	1	—	1	1	1
1/512	1	—	—	—	—	1
Total .. ..	428	356	31	29	4	8
Positive	No.	22	12	3	1	5
	Per cent.		3	3	10	50

TABLE XI  
COMPARISON OF RADIOLOGICAL RHEUMATOID ARTHRITIS HANDS AND/OR FEET WITH SHEEP CELL AGGLUTINATION TEST

SCAT Titre	Total No.	Grading of Radiological R.A. Hands and/or Feet				
		0	1	2	3	4
0	278	170	89	16	1	2
1/4	81	47	30	4	—	—
1/8	33	14	18	1	—	—
1/16	14	7	6	1	—	—
1/32	9	4	3	2	—	—
1/64	5	1	2	1	1	—
1/128	3	1	—	—	—	2
1/256	4	2	1	—	—	1
1/512	1	—	—	—	—	1
Total .. ..	428	246	149	25	2	6
Positive	No.	22	8	6	3	4
	Per cent.		3	4	12	63
						24

The interrelationship between the sheep cell test, and radiological changes Grades 1 to 4 in the hands and/or feet and in the cervical spine is shown in Fig. 4 and in Table XII (opposite); the relationship after excluding Grade 1 is also shown in the Table. In each case there is seen to be a progressive increase in the proportion having a positive sheep cell test from those without x-ray changes to those in whom both the hands and feet and the cervical spine were involved. When doubtful changes were included, a higher proportion of positive tests was found when the radiological changes were present only in the cervical spine than when they were confined to the hands and/or feet; when doubtful changes were excluded, the reverse applied. An interesting finding was that four out of six with definite radiological

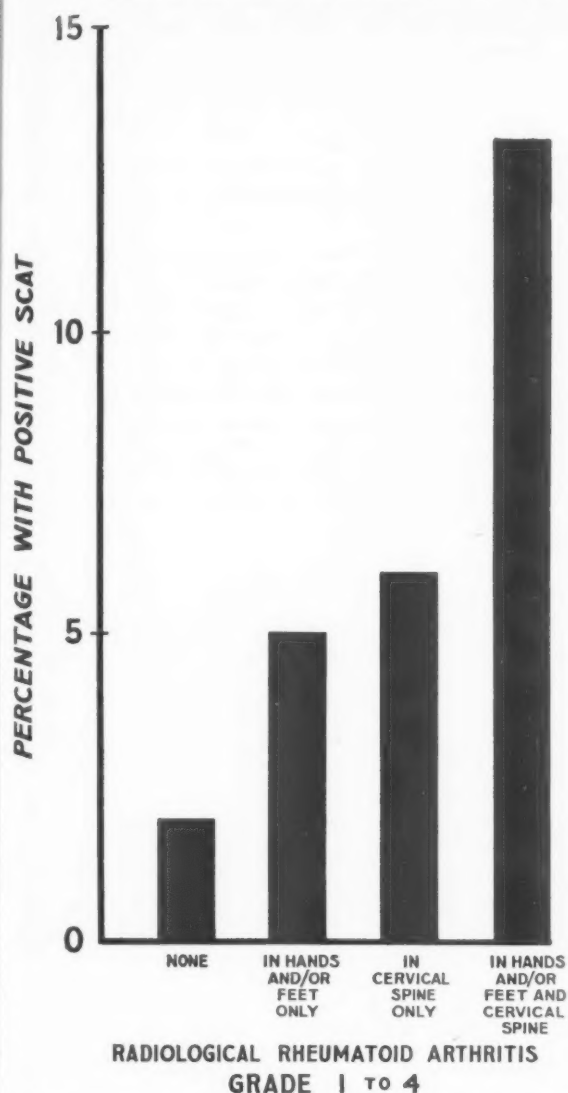


Fig. 4.—Relationship of radiological changes of rheumatoid arthritis in the cervical spine and peripheral joints to the sheep cell agglutination test.

evidence of rheumatoid arthritis at both sites gave a positive test. The correlation coefficient for the association of the sheep cell titre with radiological changes in the hands and feet is  $r = +0.25$ , in the cervical spine  $r = +0.16$ , and in both sites  $r = +0.27$ .

#### Discussion

It is apparent from the data presented that certain radiographic changes in the intervertebral disks, vertebral bodies, and apophyseal joints in the cervical spine are frequently associated with a positive sheep cell agglutination test. The characteristic disk changes (narrowing of the disk spaces

TABLE XII  
COMPARISON OF RADIOLOGICAL RHEUMATOID ARTHRITIS GRADING OF HANDS AND/OR FEET AND CERVICAL SPINE FILMS WITH SHEEP CELL AGGLUTINATION TEST RESULTS

X-ray Reading Grades		Total No.	SCAT Positive	
			No.	Percentage of Total
1-4	Hands and/or Feet without Cervical Spine	121	6	5
	Cervical Spine without Hands and/or Feet	66	4	6
	Both	61	8	13
	Neither	180	4	2
	Grand Total	428	22	5
2-4	Hands and/or Feet without Cervical Spine	27	4	15
	Cervical Spine without Hands and/or Feet	23	1	4
	Both	6	4	67
	Neither	372	13	3
	Grand Total	428	22	5

with relatively little osteophytosis of the vertebral bodies, erosion of the vertebral plates, and vertebral subluxation) were observed most frequently in the upper cervical region in the age group studied. It may be that similar changes in the lower cervical region were less frequently recognized because of the high prevalence of degenerative changes in this region in this age group. Narrowing of cervical disk spaces has been previously observed in patients whose rheumatoid arthritis began in childhood (Coss and Boots, 1946; Potter and others, 1954; Ziff and others, 1956). Gibson (1957) described two examples of destruction of cervical intervertebral disks by vascular granulation tissue arising from the underlying marrow spaces of the vertebral body in the adult form of the disease; he stated that the histological findings in the affected disks were broadly similar to those of the diarthrodial joints modified by anatomical differences between the sites.

In one of Gibson's cases, subluxation had occurred through the destroyed disk between the fourth and fifth vertebrae with resultant pressure on the spinal cord. Subluxation, usually at the atlanto-axial level, has been reported in juvenile rheumatoid arthritis (Coss and Boots, 1946; Potter and others, 1954; Werne, 1957) and atlanto-axial subluxation is seen not infrequently in severe rheumatoid arthritis in the adult (Purser and Sharp, 1958). Kersley (1956) described several examples, but otherwise subluxation lower in the cervical region does not appear to have been previously recognized as a feature of adult rheumatoid arthritis. Bony fusion of cervical apophyseal joints is a relatively common late finding in juvenile rheumatoid arthritis (Coss and Boots, 1946; Potter and others, 1954; Ziff and others, 1956) and

is occasionally encountered in patients in whom disease began in adult life (Sharp, 1957). Histological changes in spinal apophyseal joints similar to those in other diarthrodial joints affected by the disease have been observed in adult rheumatoid arthritics, but little abnormality may be discernible even in *post mortem* radiographs of isolated apophyseal joints which are the site of severe histological changes (Sharp, 1955). The difficulty encountered in identifying apophyseal joint changes in this study is therefore not surprising.

The diagnosis in the in-patients, from whose films the criteria for the radiological signs of rheumatoid arthritis of the cervical spine were derived, was largely based on the clinical findings and radiological changes in the peripheral joints, so that the failure of these cervical changes to correlate with rheumatoid arthritis as diagnosed on clinical grounds in the sample of the general population was unexpected. The correlation of the changes with a positive sheep cell test in the population sample is perhaps not surprising, as 92 per cent. of the rheumatoid in-patients tested (86 per cent. of the group as a whole) gave positive results in the test. The relationship of the cervical changes and of those in the hands and feet to the sheep cell test which was found in the population sample is of interest. It appears that each may contribute to a positive test and that if both are involved the test is more likely to be positive.

Patients with a polyarthritis of rheumatoid type may be divided by the sheep cell test into two groups: "sero-positive" and "sero-negative". This study provides no evidence of any association between the cervical changes described and sero-negative polyarthritis. The findings suggest that, in sero-positive rheumatoid arthritis of sufficient severity for the patient to be admitted to a special centre, both the peripheral joints and the cervical spine are frequently affected, but that in the general population the disease may be encountered in a form in which the spine is mainly or exclusively involved. The number of cases in this series is too small to permit of a detailed study of the symptoms associated with the spinal changes, but preliminary studies have shown that pains in the neck and shoulder region are more frequent in persons having these changes than in the general population. The clinical diagnosis of rheumatoid arthritis, as at present determined, is largely dependent on the recognition of peripheral joint changes, so that in a patient presenting with such symptoms a diagnosis of rheumatoid arthritis may not be considered. It is of course possible that the dorsal or lumbar spine may be similarly affected and give rise to chest or

back pain, but it is unlikely that many patients with this form of sero-positive rheumatoid arthritis are referred to this centre, where the majority of patients with complaints referable to the spine are seen in a special spondylitis clinic. A sheep cell test is done routinely on these patients and only 6.2 per cent. of a series of 584 patients tested gave a positive result.

It is hoped shortly to study a larger sample of the general population which will include all age groups over the age of 15 years. From this it should be possible to ascertain whether the changes observed in the upper cervical region in the age group investigated in the present study are detectable elsewhere in the cervical spine in younger subjects. It is also hoped to form a more definite impression of the clinical features of this spinal form of the disease and to obtain an estimate of its prevalence in the population as a whole.

### Summary

A series of lateral radiographs of the cervical spine from 44 hospital patients, aged 55-64, suffering from rheumatoid arthritis have been compared with a series from persons of the same age and sex distribution selected at random from the general population.

The films from rheumatoid subjects showed more narrowing of the upper cervical disks. This disk narrowing was more often associated with erosion of the vertebral plates and less often with sclerosis or osteophyte formation, and in the apophyseal joints there were more destructive changes. The films from non-rheumatoid subjects showed more proliferative changes. In rheumatoid subjects, vertebral subluxations were more frequent and more severe at all levels of the cervical spine.

Using these criteria, a series of 428 cervical radiographs from random samples of the population have been graded for the changes of cervical rheumatoid arthritis. Definite evidence of rheumatoid arthritis was found in the films of 6 per cent. of the males and 7 per cent. of the females. There was a relationship between the radiological grading for rheumatoid arthritis in the cervical spine and a positive sheep cell agglutination test.

There was little or no correlation between these radiological gradings for cervical rheumatoid arthritis and either morning stiffness or a clinical diagnosis of rheumatoid arthritis, or with a diagnosis of rheumatoid arthritis made in accordance with the criteria of the American Rheumatism Association. There was, however, an association between radiological signs of rheumatoid arthritis in the cervical spine and similar signs in the hands and feet.

A cervical form of rheumatoid arthritis without

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peripheral joint involvement may account for an important number of apparently false-positive reactions in the sheep cell agglutination test.

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## Arthrite rhumatismale cervicale

## RÉSUMÉ

On compara une série de radiographies latérales de la colonne cervicale de 44 malades hospitalisés, entre âges de 55 à 64 ans, atteints d'arthrite rhumatismale, à une série similaire de personnes d'âge et de sexe correspondants, choisies au hasard dans la population générale.

Les clichés des rhumatisants accusaient plus de rétrécissement des disques cervicaux supérieurs. Ce rétrécissement du disque était plus souvent associé à l'érosion épiphysaire et moins souvent à la sclérose ou à la formation d'ostéophytes et il y avait plus de lésions destructives dans les articulations apophysaires. Les clichés des sujets non-rhumatisants montraient plus d'altérations prolifératives. Chez les rhumatisants, les subluxations vertébrales étaient plus fréquentes et plus sévères à tous les niveaux du rachis cervical.

En prenant ces résultats pour critère, on gradua une série de 428 radiographies cervicales, pris au hasard parmi la population, du point de vue d'altérations dénotant l'arthrite rhumatismale cervicale. Des preuves définies d'arthrite rhumatismale furent trouvées dans les clichés de 6% des hommes et 7% des femmes. Il y eut un rapport entre le grade radiologique de l'arthrite

cervicale et le résultat positif de la réaction d'agglutination de globules de mouton.

Il y eut peu ou pas de corrélation entre le grade radiologique de l'arthrite rhumatismale cervicale et une rigidité matinale ou un diagnostic clinique d'arthrite rhumatismale ou même un diagnostic d'arthrite rhumatismale basé sur les critères de l'*American Rheumatism Association*. Il y eut, toutefois, une association entre les signes radiologiques d'arthrite rhumatismale au niveau des vertèbres cervicales et des signes similaires dans les mains et les pieds.

La forme cervicale de l'arthrite rhumatismale sans implication des articulations périphériques peut expliquer un grand nombre de réactions positives apparemment fausses d'agglutination de globules de mouton.

## Artritis reumatoide cervical

## SUMARIO

Se compara una serie de radiografías laterales de la columna cervical de 44 enfermos hospitalizados, entre las edades de 55 y 64 años, afectados de artritis reumatoide, y una serie de clisés similares de personas de edad y sexo correspondientes escogidos al azar en la población general.

Los clisés de los enfermos reumáticos acusaron un mayor estrechamiento de los discos cervicales superiores. Este estrechamiento se vió asociado más a una erosión epifisaria y menos a una esclerosis o a una formación de osteofitos; hubo también más lesiones destructivas en las articulaciones apofisarias. Los clisés de los sujetos non-reumáticos acusaron más alteraciones proliferativas. En los sujetos reumáticos, las subluxaciones vertebrales fueron más frecuentes y más severas en todos los niveles de la columna cervical.

Tomando estos resultados por criterio, se graduó una serie de 428 radiografías cervicales, de sujetos escogidos al azar entre la población, desde el punto de vista de alteraciones indicativas de la artritis reumatoide cervical. Signos definidos de artritis reumatoide fueron encontrados en los clisés de un 6% de los hombres y en un 7% de las mujeres. Hubo una relación entre el grado radiológico de la artritis cervical y el resultado positivo de la reacción de aglutinación de eritrocitos de oveja.

La correlación fué poca o ninguna entre el grado radiológico de la artritis reumatoide cervical y la rigidez matinal o el diagnóstico clínico de artritis reumatoide, aunque éste fuera basado sobre los criterios de la *American Rheumatism Association*. Hubo, sin embargo, una asociación entre los signos radiológicos de artritis reumatoide en la columna cervical y signos similares en las manos y los pies.

La forma cervical de la artritis reumatoide sin implicación de las articulaciones periféricas puede explicar un gran número de reacciones positivas aparentemente falsas de aglutinación de eritrocitos de oveja.



# C-REACTIVE PROTEIN IN RHEUMATIC HEART DISEASE

BY

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The behaviour of the C-reactive protein as a measure of rheumatic activity has been the subject of several publications. Most investigators have studied the C-reactive protein test in cases of frank rheumatic fever in children and there have been only isolated observations on its value in the assessment of rheumatic activity in chronic rheumatic heart disease in adults. Elster, Braunwald, and Wood (1956) suggested that the test might be helpful in the detection of subclinical rheumatic activity in such patients. Although recurrences of rheumatic fever become less frequent with advancing age, it is possible that rheumatic activity of this kind is more common in adults than is generally appreciated (Roberts, 1954; Biörck, 1955; Mortimer and Rammelkamp, 1956). Recently, Roberts (1954) stressed again that the course of rheumatic heart disease can be most appropriately described as polycyclic, phases of activity alternating with periods of apparent clinical quiescence. With this idea in mind, we have studied a group of unselected patients with rheumatic fever and rheumatic heart disease and have attempted to determine the value and limitations of the C-reactive protein test as a measure of rheumatic activity at various stages of the disease process.

## Material and Method

The 215 patients studied were divided into four groups according to the clinical picture:

(A) Twelve patients with active rheumatic carditis satisfying the criteria of Jones (1944); six of these were experiencing their first attack of carditis and the other six already had established valvular lesion.

(B) 61 patients with chronic rheumatic heart disease in whom the presence of rheumatic activity could not be established on clinical grounds. These patients were grouped together because they all showed signs of progressive deterioration and had either experienced cardiac failure before this study was undertaken, or were suffering from it while the study was being carried out.

(C) 134 Patients with chronic rheumatic heart disease who were considered clinically to be in a quiescent stage. These patients had never had cardiac failure and the size of the heart had remained unchanged for several years.

(D) Eight patients with chorea and no other rheumatic manifestation.

426 C-reactive protein tests were carried out on these 215 patients according to the method of Anderson and McCarty (1950), using commercial C-reactive protein antiserum-Schiffelin. Other tests, including the erythrocyte sedimentation rate, were carried out at the same time. The laboratory aspects and the comparative value of these tests are the subject of a separate communication (Eastham, Szekely, and Davison (1958).

## Results

The behaviour of the C-reactive protein in the four clinical groups is shown in the Table.

*Group A.*—All patients with clear evidence of active rheumatic carditis gave a positive test for C-reactive protein.

TABLE I  
C-REACTIVE PROTEIN IN RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

Clinical Group	No. of Patients	Average Age (yrs)	C-Reactive Protein	
			Present	Absent
(A) Active Carditis	12	26	12	0
(B) Chronic valvular disease No certain evidence of rheumatic activity Past or present cardiac failure	61	40	47	14
(C) Chronic valvular disease No certain evidence of rheumatic activity No cardiac failure	134	32	11	123
(D) Chorea only	8	12	0	8

Six of these patients were treated with prednisone for 10 to 73 days. Clinical improvement was rapid and the C-reactive protein disappeared from the serum in all six patients between 6 and 18 days after the start of the treatment. In four patients, the abnormal protein reappeared between 8 and 14 days after discontinuation of prednisone: in three of these the test became negative again within a fortnight without further treatment, but in the fourth patient it remained positive and she had a clinical relapse within a month.

The behaviour of the C-reactive protein in a patient treated with prednisone is illustrated in the Figure.

Six patients were treated with salicylates only and here the C-reactive protein persisted for 4 to 6 weeks.

**Group B.**—C-reactive protein was present in 47 of the 61 patients with chronic rheumatic heart disease whose cardiac condition was judged to be progressive but in whom no certain clinical criteria of rheumatic activity could be found. Of the 47 patients, 25 were experiencing cardiac failure, associated with bronchitis in four and embolic episodes in five, at the time of the initial laboratory investigation. Two further patients had embolic episodes without cardiac failure.

In seven patients the C-reactive protein test became negative after the signs of cardiac failure had disappeared, but in seven others it persisted in spite of comparable clinical improvement.

In the remaining eleven patients with cardiac failure only single tests were done.

In the two patients who had embolic episodes without cardiac failure, there was a reversal from the initial positive test to a negative within a week.

Of the fourteen patients in this group with a negative C-reactive protein test five were suffering from cardiac failure; none of these had respiratory infection or embolic episodes.

**Group C.**—Of the 134 patients with chronic rheumatic heart disease who were considered clinically to be in a quiescent stage, eleven had a positive C-reactive protein test. Two of these had bronchitis and one had a pulmonary infarct. A fourth patient had arthralgia and 6 months later developed rheumatoid arthritis. In two patients there had been a recent change from sinus rhythm to atrial fibrillation. The remaining five patients were in every way comparable to the large number of patients in this group in whom C-reactive protein was absent.

**Group D.**—In the eight patients who had chorea and no other rheumatic manifestations, the C-reactive protein test was invariably negative.

#### C-Reactive Protein and Aschoff Bodies

There were seven patients in whom auricular biopsies were available for examination after mitral valvotomy who also had pre-operative C-reactive protein determinations. Five had a positive test and in four of these Aschoff bodies were demonstrated. Aschoff bodies were also found in two patients with negative C-reactive protein tests.

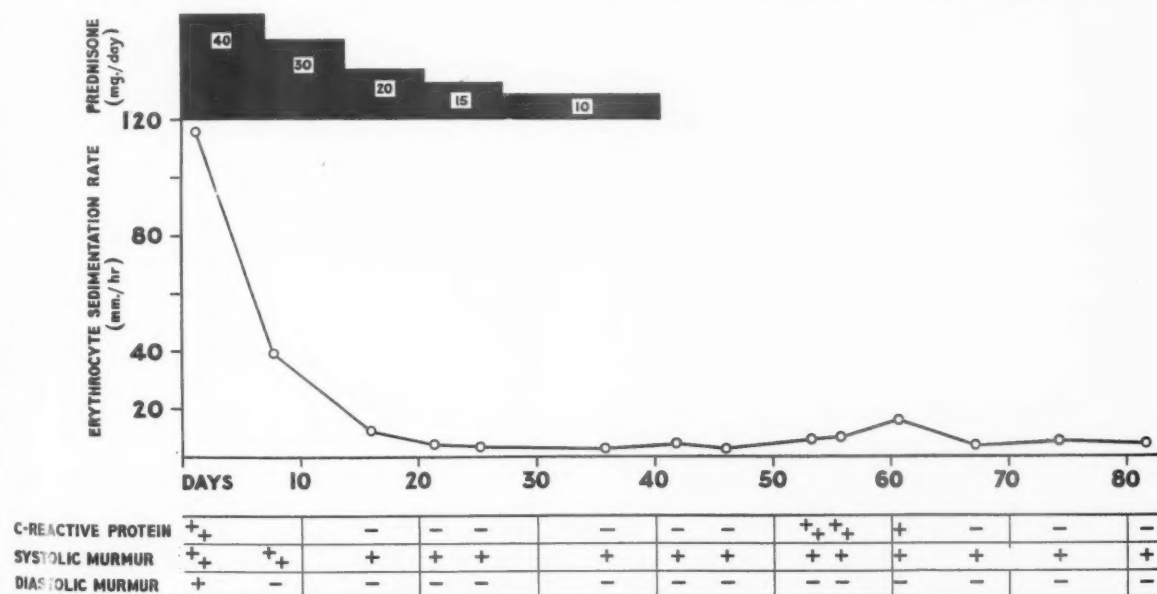


FIGURE.—Behaviour of C-reactive protein in a case of active rheumatic carditis treated with prednisone.

Two further patients came to autopsy: one had a negative C-reactive protein test in the presence of many Aschoff bodies in the left atrium and left ventricle, and in the other the C-reactive protein test was positive and no Aschoff bodies were found in the heart muscle.

### Discussion

Anderson and McCarty (1950) stated that the detection of C-reactive protein in the serum was the most consistently positive laboratory finding in the presence of rheumatic activity. A similar opinion was later expressed by Bunim, Kuttner, Baldwin, and McEwen (1952) and Stollerman, Glick, Patel, Hirschfield, and Rusoff (1953). Hill (1952) also stated that the C-reactive protein faithfully reflected the fluctuations in the activity of the disease. However, this protein has not been invariably present in active rheumatic disease (Shackman, Heffer, and Kroop, 1954). In the present series C-reactive protein could be detected in every case where the clinical findings indicated an active rheumatic process.

Treatment with prednisone led to disappearance of the C-reactive protein within 3 weeks and there was a parallel clinical improvement in all patients so treated. Similar results have been obtained by others (Bunim and others, 1952; Stollerman, Glick, and Anderson, 1954; McEwen, 1955; Bunim, 1956; Rahman and Mozziconacci, 1957). However, opinions have differed whether this indicates complete suppression of rheumatic activity or not. According to McEwen and Ziff (1955), the C-reactive protein test is not a reliable guide to rheumatic activity during hormone treatment because of the direct effect of the hormones on this protein. On the other hand, there is evidence to show that the disappearance of C-reactive protein from the serum during treatment with adreno-cortical hormones or with salicylates is due to suppression of the inflammatory process rather than to a primary effect of these agents upon the metabolism of C-reactive protein (Stollerman and others, 1954; Hedlund, Frisk, and Bucht, 1956). Stollerman and others (1953) also emphasize that the persistence of C-reactive protein during treatment indicates incomplete suppression of the inflammatory process and that treatment should be continued until the positive reaction becomes negative. Yocum and Doerner (1957) also found that large doses of hormones in rheumatic fever did not cause the C-reactive protein to disappear as long as rheumatic activity was clinically evident. Rahman and Mozziconacci (1957) found that the C-reactive protein persisted longer in patients treated with

salicylates than in the hormone-treated group, and this is in keeping with our own observations.

The C-reactive protein was found to reappear in the serum after discontinuation of hormone therapy (Ziegler and Kuttner, 1951; Stollerman and others, 1953; Shackman and others, 1954). Bunim (1956) reported that, when hormonal administration was discontinued, the C-reactive protein temporarily reappeared in 40 per cent. of cases. Rahman and Mozziconacci (1957) found a reversal of the C-reactive protein test from negative to positive in 27 per cent. of the cases. We also found that C-reactive protein reappeared after discontinuing prednisone in four cases. Dawson (1957) stated that, in those cases which relapsed, the C-reactive protein test became positive a few days before the relapse became clinically apparent. Shackman and others (1954) expressed the opinion that only continued observation for at least 3 weeks, without re-institution of therapy, can differentiate between a rebound and persisting rheumatic activity.

When chorea was the only rheumatic manifestation, the C-reactive protein was invariably absent. This is in keeping with the findings of previous investigators (Anderson and McCarty, 1950; Stollerman and others, 1953; Wood and McCarty, 1954; Dawson, 1957; Rahman and Mozziconacci, 1957). Shackman and others (1954) reported two patients with chorea who had a positive C-reactive protein test but both had concurrent carditis. These authors stressed that a positive test in chorea should suggest an associated carditis and that a negative test is presumptive evidence of its absence.

The present observations suggest that single C-reactive protein determinations in chronic rheumatic heart disease in the absence of clinical evidence of rheumatic activity may be misleading, but that repeated tests interpreted in conjunction with the clinical progress may be helpful in the assessment and management of these cases. Those patients in whom the disease progressed very little, if at all, over a period of years, as judged by the lack of symptoms, absence of progressive cardiac enlargement, and cardiac failure, showed as a rule repeatedly negative C-reactive protein tests. Shackman and others (1954) also stated that a negative C-reactive protein test was an accurate measure of the inactive state. A clinical analysis of the cases included in Group B showed that the 47 patients who had an initial or persistent positive C-reactive protein test represented a more advanced condition within the group, as judged by exercise tolerance and cardiac size, than the fourteen patients without C-reactive protein. In view of the non-specific nature of the C-reactive protein test, we do not feel justified in concluding



how many, if any, of these patients had in fact active rheumatic carditis. (However, it would appear from the present study that a persistently positive C-reactive protein test in chronic rheumatic heart disease is a significant finding because it is more often than not associated with progressive cardiac enlargement and clinical deterioration.)

Although C-reactive protein is usually present in congestive cardiac failure with rheumatic activity (Bywaters, 1956), the findings of Elster and others (1956) tend to show that congestive heart failure *per se* may give rise to a positive test. On the other hand, Stollerman and others (1953) and McEwen and Ziff (1955) believe that congestive cardiac failure is not responsible for the appearance of this protein. In the present series, C-reactive protein disappeared from the serum in several patients after the signs of cardiac failure had cleared up; in other patients it persisted in spite of comparable clinical improvement, and yet in other cases it was not present at all during the stage of cardiac failure. These findings suggest that congestive cardiac failure *per se* is not likely to be responsible for the production of C-reactive protein. Embolic episodes or respiratory infection are known to account for a positive test (Hedlund, 1947; Roantree and Rantz, 1955; Elster and others, 1956; Yocum and Doerner, 1957), and these complications were present in some of our patients.

Several patients with a positive C-reactive protein test were pregnant, but in our experience pregnancy does not influence the behaviour of this protein. In 48 normal pregnant women at various stages of their pregnancy, the test was invariably negative. This is in agreement with the findings of Hedlund (1947) and Shetlar, Bullock, Shetlar, and Payne (1955).

Elster and Wood (1955) reported on the lack of correlation between pre-operative C-reactive protein tests and the presence of Aschoff bodies in auricular biopsies obtained from patients undergoing mitral valve surgery. We have also encountered instances of negative C-reactive protein tests in the presence of Aschoff bodies. Elster and Wood (1955) suggest that, in these cases, the pathological process is not sufficiently active to lead to the production of C-reactive protein, and that the degree of rheumatic activity may have little or no clinical significance.

#### Summary

The behaviour of C-reactive protein was studied in patients with rheumatic fever and rheumatic heart disease at various stages of the disease process.

C-reactive protein was always present in active

rheumatic carditis and proved a useful guide in the management of these cases.

In cases of isolated chorea, C-reactive protein was invariably absent and this appeared to be good evidence of the absence of concurrent carditis.

The value and limitations of the test in chronic heart disease in the absence of obvious clinical evidence of rheumatic activity are discussed.

Our thanks are due to Dr. W. G. A. Swan and Dr. F. Jackson for their help and criticism. We should also like to thank Dr. G. Davison, Dr. G. Richardson, and Dr. C. Cooper for allowing us to study some of their patients. The mitral valve operations referred to in the paper were performed by Mr. G. A. Mason. We are grateful to Dr. I. Rannie for the reports on the auricular biopsies and to Dr. B. E. Tomlinson for the autopsy findings.

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#### Protéine C-réactive dans la maladie de Bouillaud

##### RÉSUMÉ

On étudia le comportement de la protéine C-réactive chez des malades atteints de maladie de Bouillaud à de différentes périodes évolutives.

La protéine C-réactive fut toujours présente dans la cardite rhumatismale active et se révéla utile dans le maniement de ces cas.

Dans des cas de chorée seule, la protéine C-réactive fut invariablement absente, fournissant ainsi une preuve d'absence d'une cardite concomitante.

On discute la valeur et les limitations de cette épreuve dans la maladie rhumatismale chronique du coeur en



l'absence de preuves cliniques apparentes d'activité rhumatismale.

**Proteína C-reactiva en la enfermedad de Bouillaud**

**SUMARIO**

Se estudió el comportamiento de la proteína C-reactiva en los pacientes con la enfermedad de Bouillaud en diferentes periodos evolutivos.

La proteína C-reactiva se pudo siempre demostrar

en la presencia de carditis reumática activa y se reveló útil en el manejo de estos casos.

En casos de corea sola, la ausencia invariable de la proteína C-reactiva ofrecía una prueba válida de ausencia de una carditis concomitante.

Se discute el valor y las limitaciones de esta reacción en la enfermedad reumática crónica del corazón en la ausencia de pruebas clínicas aparentes de actividad reumática.

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## COMPARISON OF THE ERYTHROCYTE SEDIMENTATION RATE, C-REACTIVE PROTEIN, SERUM DIPHENYLAMINE, AND TETRAMMONIUM TESTS IN RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

BY

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The difficulty in assessing the activity of the disease process in rheumatic fever and rheumatic heart disease is apparent from the large number of laboratory tests which have been used from time to time. In a previous study (Eastham, Szekely, and Davison, 1958) we have attempted to assess the value and limitations of the C-reactive protein test as a measure of rheumatic activity in a group of unselected cases of rheumatic fever and rheumatic heart disease. In the present study, using the same clinical material, we have correlated four laboratory tests in the hope that it might be possible to demonstrate a distinct advantage of one test over the others.

In acute rheumatic fever, serum electrophoresis shows that the albumin content falls, while alpha-1, alpha-2 and gamma globulin concentrations rise (Dole, Watson, and Rothbard, 1945). Ernstene (1930) showed that plasma fibrinogen concentration rose and the haematocrit level fell. According to Jackson, Kelly, Smith, Wang, and Routh (1953), these changes are reflected in the rise in the erythrocyte sedimentation rate.

Roantree and Rantz (1955) showed that C-reactive protein occurred in the serum early in the course of acute inflammation. Coburn, Moore, and Haninger (1953) demonstrated that the serum diphenylamine reaction paralleled the erythrocyte sedimentation rate, and Jacox (1951) showed a similar correlation between the serum tetrammonium turbidity and the erythrocyte sedimentation rate in cases of rheumatic fever.

The last two tests were, therefore, selected for comparison with the erythrocyte sedimentation rate and the serum C-reactive protein in our series.

### Methods and Material

I. The erythrocyte sedimentation rate (E.S.R.) was read at one hour in 200-mm. tubes of 2.5 mm. internal diameter (Westergren, 1921) using citrate solution as already described. Any reading of more than 10 mm. in one hour was regarded as abnormal.

II. The serum tetrammonium turbidity reaction (TET) was estimated by the method of Jacox (1951). The turbidity was read in 1 cm. cells in a twin-cell Spekker absorptiometer, using an Ilford spectrum violet filter No. 601. Cetyl-dimethyl-benzyl-ammonium chloride was used in place of octyl-dimethyl-benzyl-ammonium chloride, since it has an identical effect on serum protein (Jacox, 1953). The barium sulphate standard suspension (Jacox, 1951) gave an extinction value of 0.585. The upper limit for normal serum was taken as 0.295.

III. The serum diphenylamine reaction (DIP) was estimated by the method of Coburn and others (1953), using the sensitive diphenylamine reagent of Ayala, Moore, and Hess (1951). Correction for the serum blank was not made in view of the findings of Coburn, Bates, Hahn, and Murphy (1956). The reaction was read at 530 mμ in 1 cm. cells in a Unicam S.P. 600 spectrophotometer. The instrument readings were brought into line with those of Coburn and his co-workers. This was done with the help of Dr. E. L. Hess, Ph.D., who kindly supplied a suitable calibration graph; from this reference sucrose standards were prepared. The normal range of coefficient of extinction for our instrument was 0.246-0.379, with an average of 0.330 (this value corresponds to the colour given by a 0.106 g. per cent. solution of pure sucrose).

IV. A capillary qualitative test for the presence of serum C-reactive protein was made (Anderson and McCarty, 1950), using C-reactive protein antiserum—Schieffelin.

The four tests were performed on 362 blood samples taken from 191 patients. 182 cases, out of the 191 cases, on whom all four laboratory tests were performed, were divided clinically into the following groups:

- (1) *Active rheumatic carditis* (11 cases)
- (2) *Chronic valvular heart disease*. No certain evidence of rheumatic activity, but past or present cardiac failure (50 cases)
- (3) *Chronic valvular heart disease*. No certain evidence of rheumatic activity and no past or present cardiac failure (114 cases)
- (4) *Chorea* (7 cases)
- (5) *Non-rheumatic* (9 cases):
 

Congestive cardiac failure	..	7
Rheumatoid arthritis	..	1
Erythema nodosum	..	1
- (6) *Normal pregnant women*.—Sera from 48 cases were examined using three of the tests, but on these no erythrocyte sedimentation rate estimations were made.

In 23 cases, four or more serial blood samples were tested over a period of weeks.

### Results

Fig. 1 shows the results obtained from one patient over a period of 360 days, and demonstrates similar trends in the tests used. When the serum diphenyl-

amine and tetrammonium reactions are compared as in Fig. 2 (opposite), only a very rough direct correlation is apparent.

None of the sera from the 48 pregnant women contained C-reactive protein; the range for the diphenylamine reaction with the sera was from 0.189 to 0.357 (mean 0.252); the corresponding range for the tetrammonium reaction was from 0.038 to 0.290 (mean 0.170).

When the serum diphenylamine reaction and erythrocyte sedimentation rate were compared no simple correlation was seen. Very similar results were obtained when the serum tetrammonium reaction and erythrocyte sedimentation rate were compared. Although the majority of sera gave negative results with the diphenylamine reaction and the tetrammonium reaction, this was certainly not the case with either the erythrocyte sedimentation rate or the C-reactive protein (Table I, opposite).

Fig. 3 (overleaf) shows the haemoglobin concentration, corresponding erythrocyte sedimentation rate, and presence or absence of C-reactive protein in each of the 362 blood samples tested.

The numbers of positive and negative C-reactive proteins at various erythrocyte sedimentation levels are shown in Table II (overleaf).

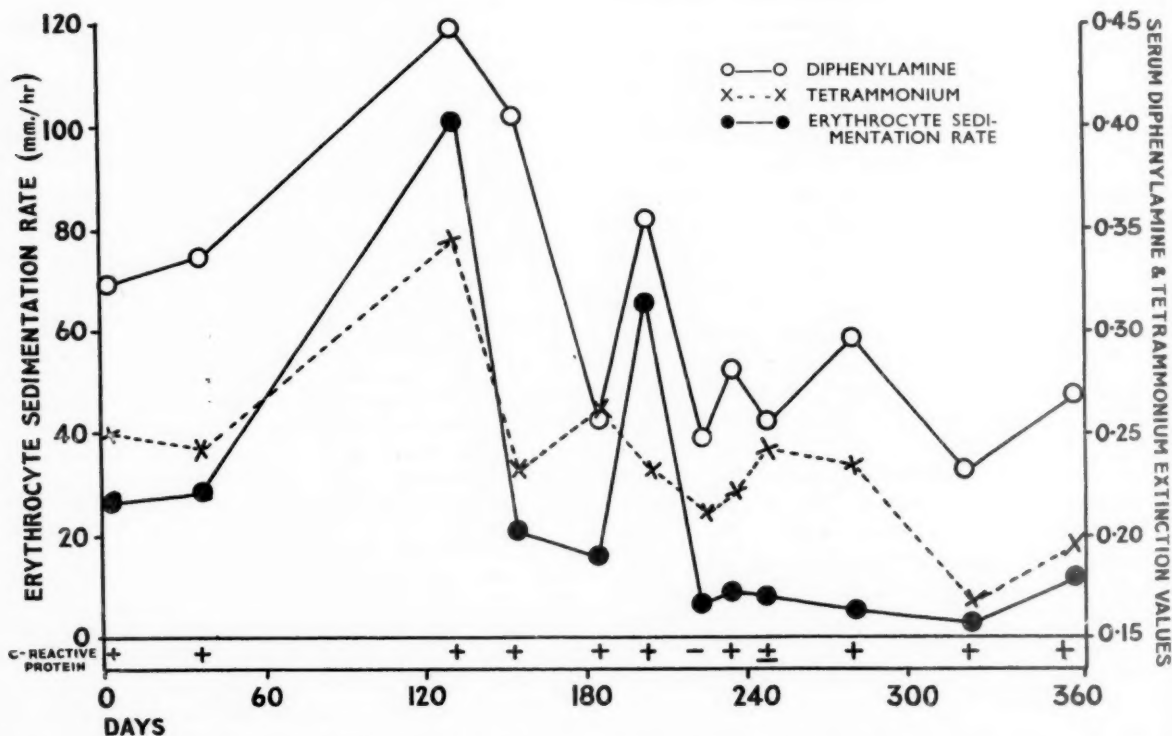


Fig. 1.—Serial readings of erythrocyte sedimentation rate, C-reactive protein, tetrammonium, and diphenylamine reactions in a case of active rheumatic carditis over a period of 360 days.

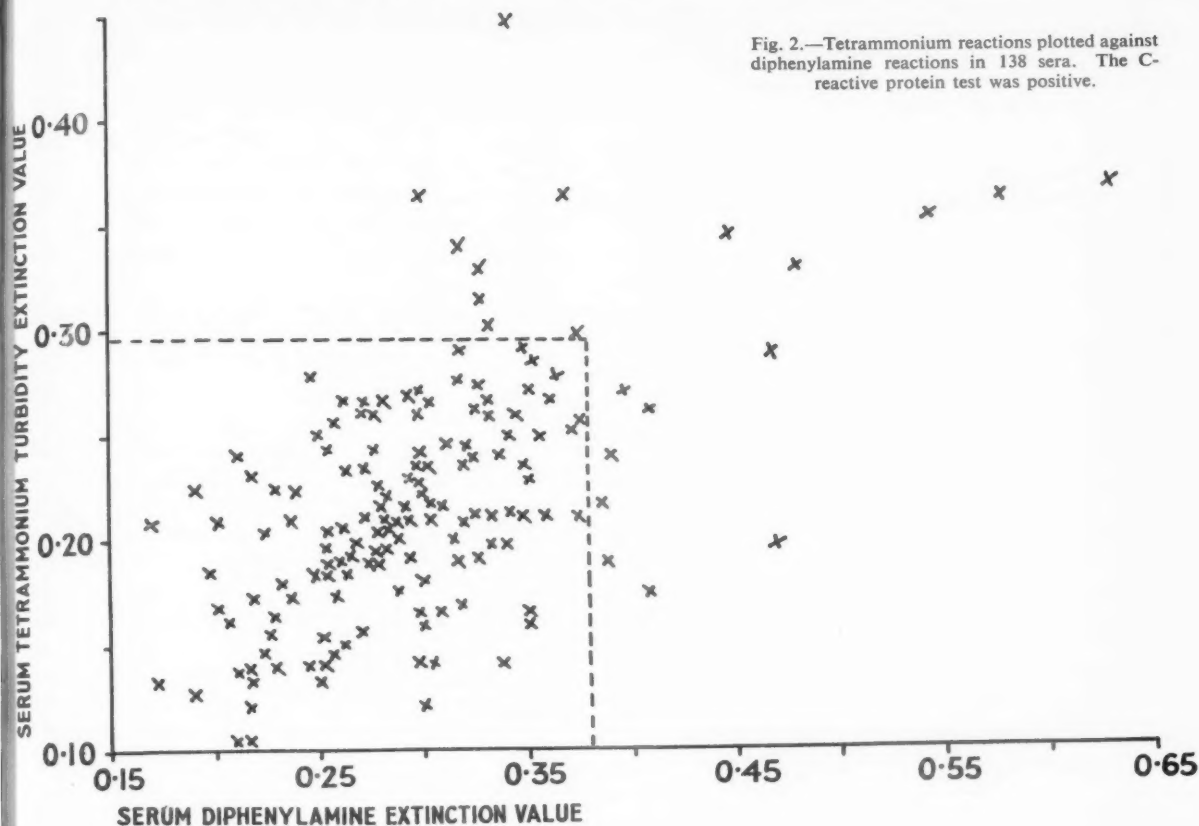


Fig. 2.—Tetrammonium reactions plotted against diphenylamine reactions in 138 sera. The C-reactive protein test was positive.

TABLE I

Group	Erythrocyte Sedimentation Rate		C-reactive Protein		Diphenylamine Reaction		Tetrammonium Reaction		Total	Pregnancy
	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive		
(1) Active Carditis ..	0	11	0	11	8	3	7	4	11	Non-pregnant
(2) Chronic Valvular Disease ..	15	28	13	30	39	4	41	2	43	Non-pregnant
Cardiac Failure at Some Time in Past or Present	0	7	3	4	7	0	7	0	7	Pregnant
(3) Chronic Valvular Disease ..	52	42	87	7	94	0	94	0	94	Non-pregnant
No Cardiac Failure at Any Time	3	17	17	3	20	0	20	0	20	Pregnant
(4) Chorea ..	3	4	7	0	6	1	7	0	7	Non-pregnant
(5) Non-Rheumatic Cases ..	4	5	3	6	8	1	8	1	9	Non-pregnant

### Discussion

The diphenylamine reaction apparently depends on sialic acid, which is derived from serum mucoprotein (Ayala and others, 1951; Coburn and others, 1956; Hess, Hahn, and Ayala, 1956; Werner and

Odin, 1952), and mucoprotein is mainly associated with the serum alpha globulin fraction (Linko and Waris, 1955). The diphenylamine reaction should, therefore, reflect mainly changes in alpha globulin, and more particularly in the alpha-1 fraction,



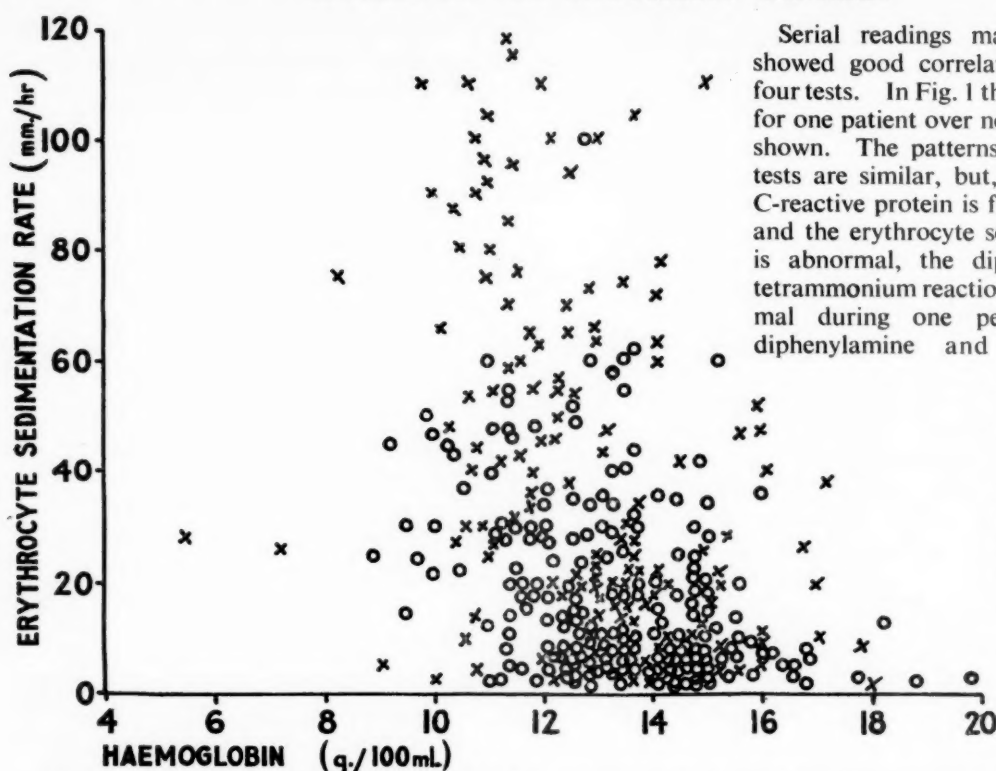


Fig. 3.—Erythrocyte sedimentation rate readings plotted against corresponding haemoglobin concentrations in 362 blood samples.  
x=Positive C-reactive Protein. O=Negative C-reactive Protein

TABLE II

C-Reactive Protein	Erythrocyte Sedimentation Rate (mm./hr)					Total Sera
	0-15	16-30	31-45	46-60	61 Upwards	
Positive	38	30	16	17	37	138
Negative	128	58	21	15	2	224

although the protein-bound polysaccharide present in the gamma globulin fraction must have an effect.

Coburn and others (1953) found that the diphenylamine reaction correlated well with the erythrocyte sedimentation rate in cases of rheumatic fever, and subsequently claimed that it was a more useful test than either the erythrocyte sedimentation rate or the C-reactive protein (Coburn and others, 1956).

The tetrammonium reaction of Jacox (1951) depends almost entirely on the alpha globulin concentration in the serum (Saifer and Zymaris, 1956). It was found by Jacox and Gale (1951) that it could be used as a non-specific test of "acute phase serum", correlating well with the erythrocyte sedimentation rate and the serum bacteriocidal activity on *B. subtilis* in cases of acute rheumatic fever.

Serial readings made in 23 cases showed good correlation between the four tests. In Fig. 1 the results obtained for one patient over nearly one year are shown. The patterns followed by the tests are similar, but, while the serum C-reactive protein is frequently positive and the erythrocyte sedimentation rate is abnormal, the diphenylamine and tetrammonium reactions are only abnormal during one period. Since the diphenylamine and tetrammonium

reactions appear to follow similar courses in serial readings on one case, it seemed possible that the two tests would correlate directly in a series of random readings. This should apply particularly in the early stages of rheumatic activity, since the alpha globulin increases before the

gamma globulin fraction and the tetrammonium reaction is known to depend almost entirely on the alpha globulin, whilst the diphenylamine reaction is influenced by changes in both alpha and gamma globulin.

Fig. 2 shows that direct correlation may be considered to be present, but that the degree of relationship is poor. Only three sera with negative C-reactive protein tests were outside the normal limits for the other two tests.

Although Yocum and Doerner (1957) claim that serum C-reactive protein migrates with the beta globulin fraction, and Hedlund and Brattsten (1955) are of the opinion that it migrates with gamma globulin, it is more probable that C-reactive protein, on electrophoresis, runs with the alpha-1 globulin fraction (Hedlund, 1947; Perlman, Bullowa, and Goodkind, 1943; Shackman, Heffer, and Kroop, 1954). Wood and McCarty (1951) found that the serum test was positive when 1 mg. C-reactive protein per 100 ml. serum was present. In acute cases of rheumatic fever, the level could rise to more than 33 mg. per 100 ml. This amount is still only a fraction of the total alpha globulin.

Fearnley, Pirkis, de Coek, Lackner, and Meanock

(1955) used the diphenylamine reaction in the assessment of activity in rheumatoid arthritis, and they found a wide overlap of diphenylamine readings when normal controls were compared with active cases. They also found that the diphenylamine reaction was not abnormal in any of the active cases in which the erythrocyte sedimentation rate was normal. While the diphenylamine reaction follows the pattern of the erythrocyte sedimentation rate in any one case of acute rheumatism (Fig. 1), one reading alone cannot be used with any degree of certainty to detect activity, unless it is grossly in excess of the upper limits of normal. This also applies to the tetrammonium reaction. The erythrocyte sedimentation rate and diphenylamine reaction in 362 blood samples demonstrated that, within the normal range of the diphenylamine reaction, grossly abnormal erythrocyte sedimentation rate readings occurred which could not be explained by the presence of anaemia alone. No simple correlation between the diphenylamine reaction and the erythrocyte sedimentation rate was apparent. Similar results were obtained when the tetrammonium reaction and the erythrocyte sedimentation rate were compared in the same blood samples.

The erythrocyte sedimentation rate is affected by the plasma fibrinogen and globulin concentrations (particularly alpha and gamma globulin fractions) and by the packed cell volume. With the Westergren method, the influence of the latter factor is reduced, since whole blood is diluted with sodium citrate solution and the use of 200-mm. columns delays the onset of packing. In Fig. 3 the haemoglobin concentration is plotted against the erythrocyte sedimentation rate of the blood specimens examined; with a haemoglobin concentration of 15 g. per 100 ml., a reading of 110 mm./1 hr is seen to be possible (a corresponding Wintrobe reading could not exceed 45 mm./hr).

The findings in Table I strongly suggest that erythrocyte sedimentation rate and C-reactive protein readings are much more sensitive than the diphenylamine and tetrammonium reactions. Thus, in the "active carditis" group of eleven cases, the erythrocyte sedimentation rate was raised and the C-reactive protein was positive in all cases, whereas the diphenylamine and tetrammonium reactions were abnormal on only three and four cases respectively. In the second group of fifty cases of "chronic valvular disease with a history of cardiac failure at some time", the erythrocyte sedimentation rate and C-reactive protein were more frequently positive than either of the other two tests. The erythrocyte sedimentation rate was more frequently positive

than the other tests in the third group of 114 cases of "chronic valvular disease with no history of cardiac failure". In particular, the erythrocyte sedimentation rate was raised in seventeen out of twenty of the pregnant women in this group (nine of the pregnant women had haemoglobin concentrations of less than 12 g./100 ml.). The erythrocyte sedimentation rate was also raised in 42 out of the 94 non-pregnant women in this group, and again, nine of the cases with a raised erythrocyte sedimentation rate had haemoglobin concentrations of less than 12 g./100 ml. Thus anaemia is not the complete cause of a raised erythrocyte sedimentation rate, even though evidence of acute inflammation, as shown by positive C-reactive protein tests in ten cases in this group, is lacking in the remaining 49 cases. In the absence of anaemia, the presence of a raised erythrocyte sedimentation rate must be regarded as pathological. It is known that, on recovery from an acute inflammatory process, the C-reactive protein becomes negative before the erythrocyte sedimentation rate returns to normal, and therefore it must be assumed that these cases were recovering from an acute inflammatory condition or had reached a chronic inflammatory phase. In this third group of cases the diphenylamine and tetrammonium reactions were all negative.

In the fourth group the total of seven cases of chorea is too small for any accurate conclusion to be drawn; no case had a positive C-reactive protein, whereas four had a raised erythrocyte sedimentation rate. Table II shows that the majority of blood samples contain C-reactive protein only when high erythrocyte sedimentation rate readings are obtained.

Other workers have compared a number of the tests used to detect serum changes in acute inflammation. Harris, Friedman, and Tang (1957) compared four such tests, and found that the erythrocyte sedimentation rate fell with the onset of cardiac failure. With hormone therapy, the erythrocyte sedimentation rate fell, the C-reactive protein became negative, and the antistreptolysin-"O" titre fell; on cessation of treatment, both the erythrocyte sedimentation rate and C-reactive protein reaction showed a "rebound" phenomenon. These authors also observed that, after the C-reactive protein test became negative, the serum mucoprotein already being normal, the erythrocyte sedimentation rate remained abnormal, particularly in adolescent girls.

In a series of observations, Adams (1956) compared the serum mucoprotein, serum C-reactive protein, serum non-glucosamine polysaccharide, and antistreptolysin-"O" titre, and concluded that the C-reactive protein was only remotely related to the concentration of the mucoprotein and non-glucosa-

mine polysaccharide. He also observed that there existed a direct relationship between these two latter entities, but that the relationship was not consistent.

Comparison of a series of ten tests by Müller and Kähler (1956) showed that the C-reactive protein, erythrocyte sedimentation rate, and serum copper levels were reliable indices of activity. The serum iron, Takata Ara reaction, Weltmann reaction, thymol turbidity, total white cell count, polymorphonuclear lobe count, and body temperature measurement, were much less reliable. The body temperature was the most useful and the Takata Ara reaction the least useful of these latter tests. The tests listed by Fischel (1957) attempt to estimate the numerous complicated changes which occur in the blood at different rates during the course of an inflammatory process. Since these are essentially non-specific in nature, and the exact stage of the disease process is not known in any given case, it is hardly surprising that simple direct correlation has not been found.

Critical appraisal of the results obtained by other workers and of our own experience suggests that the two most useful tests are those which are most simply performed, namely, the erythrocyte sedimentation rate and the C-reactive protein reaction.

### Summary

The Westergren erythrocyte sedimentation rate, serum C-reactive protein test, serum diphenylamine reaction, and serum tetrammonium turbidity reaction, were compared in 362 samples of serum from 217 patients, with the following results:

- (1) The serum diphenylamine reaction and tetrammonium turbidity reaction are not sensitive enough to determine the presence or absence of rheumatic activity.
- (2) The erythrocyte sedimentation rate and C-reactive protein test appear to be much more sensitive, and are more easily and rapidly performed.
- (3) The erythrocyte sedimentation rate is more frequently abnormal in negative cases than the C-reactive protein test, and is influenced by both anaemia and polycythaemia.
- (4) Since the C-reactive protein reaction detects 1 mg. per 100 ml. serum, it may well be too sensitive, although the knowledge that a patient's serum contains no C-reactive protein is very useful.

Similar comparisons of tests used in the assessment of activity of the rheumatic process are discussed.

We are grateful to Drs. George Davison, George Richardson, and Christine Cooper for allowing us to study some of their cases. We are also indebted to Dr. S. Murray, Director of the Regional Blood Transfusion Centre, Newcastle-upon-Tyne, for the 48 control sera from normal pregnant women.

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### Comparaison de la vitesse de sédimentation érythrocytaire et des réactions à la protéine C-réactive, à la diphenylamine et au tetrammonium dans la maladie de Bouillaud

#### RÉSUMÉ

La vitesse de sédimentation érythrocytaire (Westergren), la réaction à la protéine C-réactive, la réaction à la diphenylamine et la réaction de turbidité au tetrammonium furent comparées en 362 prélèvements de sang de 217 malades, avec des résultats suivants:

- (1) La réaction à la diphenylamine et la réaction de turbidité au tetrammonium ne sont pas assez sensibles pour déterminer la présence ou l'absence d'une activité rhumatismale.
- (2) La vitesse de sédimentation érythrocytaire et la réaction à la protéine C-réactive semblent être beaucoup plus sensibles, et plus faciles et rapides.
- (3) La vitesse de sédimentation érythrocytaire est plus souvent anormale dans des cas négatifs que la réaction à la protéine C-réactive et est influencée aussi bien par une anémie que par une polycytémie.
- (4) La réaction à la protéine C-réactive décèle 1 mg. par 100 cc. de sérum et il se peut bien qu'elle soit trop sensible, mais il est utile de savoir que le sérum du malade ne contient pas de protéine C-réactive.

On discute des comparaisons similaires des réactions employées dans l'évaluation de l'activité du processus rhumatismal.

**Comparación de la velocidad de sedimentación eritrocitaria y de las reacciones a la proteína C-reactiva, a la difenilamina y al tetramonio en la enfermedad de Bouillaud**

**SUMARIO**

La velocidad de sedimentación globular (Westergren), la reacción a la proteína C-reactiva, la reacción a la difenilamina y la reacción de turbiedad al tetramonio fueron comparadas en 362 muestras de sangre de 217 enfermos, con los resultados siguientes:

(1) La reacción a la difenilamina y la reacción de turbiedad al tetramonio no son bastante sensibles para determinar la presencia o la ausencia de la actividad reumática.

(2) La velocidad de sedimentación eritrocitaria y la reacción a la proteína C-reactiva parecen ser mucho más sensibles y de realización más fácil y rápida.

(3) La velocidad de sedimentación eritrocitaria es más a menudo anormal en casos negativos que la reacción a la proteína C-reactiva y se ve afectada tanto por la anemia como por la policitemia.

(4) La reacción a la proteína C-reactiva revela 1 mg. por 100 cc. de suero y es, quizás, demasiado sensible, pero el conocimiento de que el suero de un enfermo no contiene proteína C-reactiva es útil.

Se discuten similares comparaciones de reacciones empleadas en la valoración de la actividad del proceso reumático.



## VALUE OF URICOSURIC AGENTS AND IN PARTICULAR OF G.28 315 IN GOUT

BY

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The value of uricosuric agents in the reduction of tophi was shown by Gutman and Yü (1957) to be marked in 36 of 82 cases of tophaceous gout and definitely present in 67. To be effective salicylates had to be used in large doses which were not then free from the risk of causing mental and haemorrhagic complications. Benemid (probenecid) produced rashes in 5 per cent. and severe gastritis in 8 per cent. of patients, and in 10 per cent. it increased the number of acute attacks during its early administration. Some pain in the loins or gravel occurred in 9 per cent. of cases, usually when some evidence of calculi had already been noted.

Phenylbutazone (Butazolidin) has only a minimal uricosuric effect in long-term therapeutic dosage, but has a strong antiphlogistic effect in gout. Following its administration, two main metabolites have been found in the urine, G.27 202 (which is antiphlogistic and causes salt retention) and G.28 231 (which is uricosuric) (Fig. 1, opposite). This suggested that modification of the butyl side-chain of phenylbutazone might alter the uric acid excretory potency. Working on this hypothesis, a substance G.25 671 was discovered; this increased the excretion of uric acid but was toxic in some 10 per cent. of cases. Its sulphonyl metabolite, however, was still more potent and less toxic and was designated G.28 315 (Burns, 1957). It is this substance which is the subject of this investigation.

G.28 315 is rapidly absorbed and has a half-life of 3 hours. It must therefore be administered not less frequently than four times a day to be effective. It has no effect on inulin clearance, but urate and P.A.S. clearance is inhibited, suggesting that it causes no change in glomerular filtration but reduces tubular transport of certain substances (Burns, Yü, Ritterband, Perel, Gutman, and Brodie, 1957).

It has been pointed out that uricosuric effect appears to vary as the acidity of the Butazolidin-like compound, phenylbutazone having a *cp* of 4.5, G.25 671 of 3.9, and G.28 315 of 2.9. This suggests that yet another analogue, G.23 with a *cp*

of 2.2, may also be of interest from this point of view.

Gutman and Yü (1957) found that, using G.25 671, four out of 65 cases produced a rash and that in five there were gastric complications. In only two out of thirty patients given G.28 315 (0.4-0.6 g. daily) was dyspepsia a serious symptom. No other toxic complications were found. With G.25 671 some antiphlogistic as well as uricosuric effect was noted.

Ogryzlo and Harrison (1957), on comparison of individual cases, suggested that Benemid 3 g., aspirin 6 g., phenylbutazone 1 g., G.25 671 1 g., and G.28 315 0.5 g. have approximately the same uricosuric effect. In eleven cases treated with 0.5 g. G.28 315, there were no toxic complications.

It was decided to make a clinical appraisal of G.28 315, its uricosuric action, its effect on the plasma uric acid, its possible toxicity, and on its optimal method of administration. A series of fifteen cases of gout (12 men and 3 women) were hospitalized. Their renal function was examined and they were placed on a control period of estimation of urinary uric acid for 7 days, 1.0 g. Benemid for 3 days, and 1.5 g. Benemid for 4 days. After this there was another control period of 7 days, followed by the administration of G.28 315 100 mg. four times daily for 7 days, and then 200 mg. four times daily for a further week. The patients were then discharged from hospital on a dosage of 400 mg. daily and were seen at monthly intervals for clinical and biochemical check. It has been shown (Kersley, Mandel, and Bene, 1951) that colchicine has no effect on uric acid excretion, and therefore in all cases 1 mg. colchicine per day was administered for the whole period in order to avoid as much as possible the complication of acute attacks. Where acute attacks, not controlled by the colchicine, appeared during the trial, phenylbutazone 600 mg. daily was administered for 2 days only and this always proved effective.

During the trial a normal diet with plenty of fluids was given, excluding only foods of very high purine

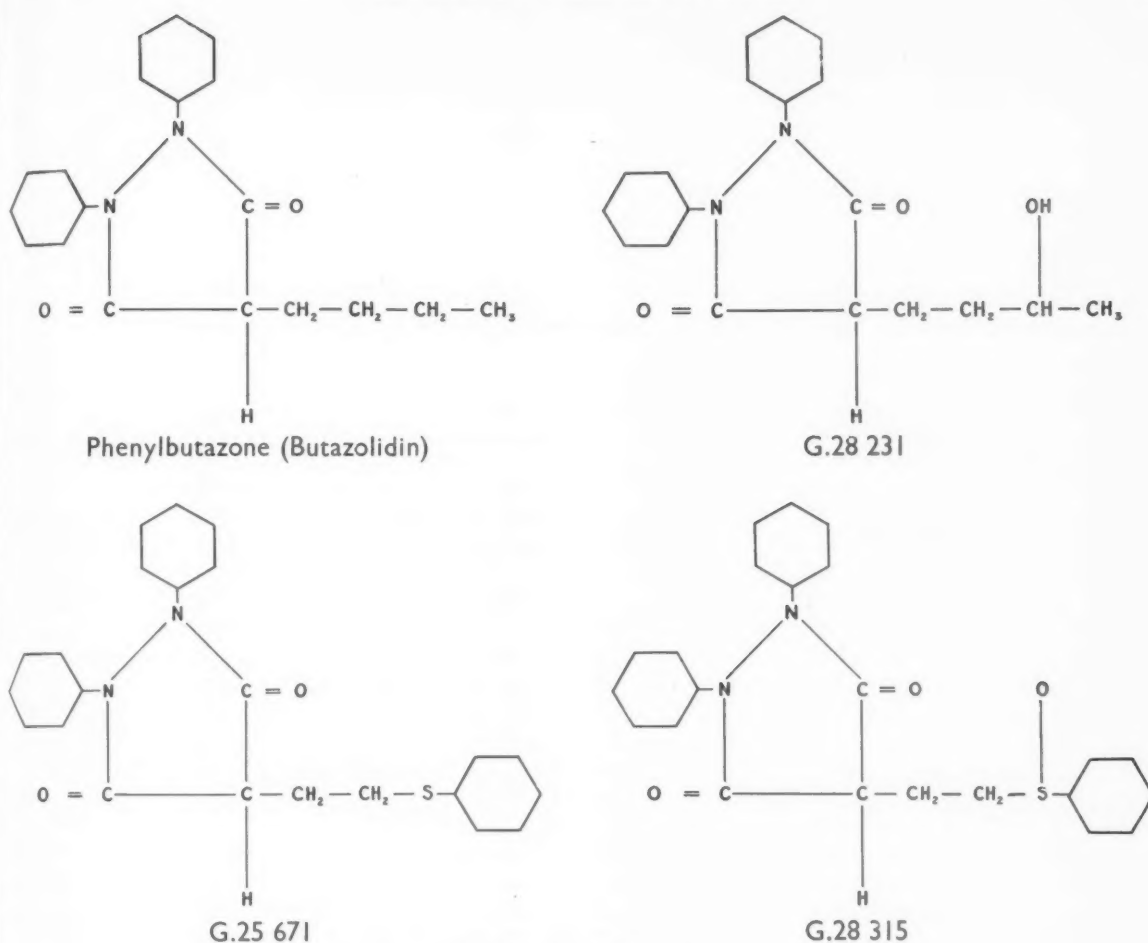


Fig. 1.—Chemical formulae.

content such as sweetbreads, fish roes, liver, kidney, etc. Urinary uric acid estimations were made by a modification of Folin's method (Bidmead, 1951).

In two cases in which 3.5 g. aspirin had previously been given—where some painful osteo-arthritis was a complication—this was replaced by pethidine temporarily for the control period. Two cases with slightly impaired renal function were similarly treated but are considered separately. White cell counts and complete urinary analyses were carried out periodically. In ten cases, after a period of continuous G.28 315 administration, the total weekly urinary excretion of uric acid was compared with that obtained by intermittent administration, *i.e.* for the first 3 days of each week. The effect of giving aspirin at the same time as G.28 315 was examined in nine cases in view of the antagonistic effect of aspirin and Benemid.

Table I (overleaf) shows the mean daily excretion

of uric acid of thirteen patients taking a daily dose of 400 and/or 800 mg. G.28 315 compared with the average levels in the control period. In seven cases a comparison is also made with the effect of 1 and 1.5 g. Benemid.

In all cases there was an increase in excretion of uric acid on giving 400 mg. of G.28 315, which was highly significant in ten and significant in the mean values for all thirteen cases. There was a further significant increase in excretion in three of five cases on raising the dosage to 800 mg., the average increase for the five also being significant. The administration of 400 mg. G.28 315 gave a greater increase in uric acid excretion than Benemid in five of the seven cases so tested, but the increase was significant in only two cases. Two patients showed little response to Benemid, but one responded to 400 mg. of G.28 315 and both to 800 mg. The average daily control excretion was 551 mg., which

TABLE I

EFFECT OF BENEMID AND G.28 315 ON MEAN URIC ACID EXCRETION OF PATIENTS WITH GOUT

Patient No.	Sex	Uric Acid Excretion (mg./24 hrs)			
		Control 5 days	Treatment (g./24 hrs)		
			Benemid (1-1.5) 7 days	G.28 (0.4) 7 days	G.28 (0.8) 7 days
1	F	549	719	688	804
2	M	521	653	752	815
3	M	506	820	869	1,047
4	M	774	1,081	1,105	1,291
5	M	722	1,059	1,050	1,253
6	M	326	554	800	
7	M	673	890	1,138	
Mean		581	825	914	1,042
8	F	435		794	
9	M	719		1,372	
10	M	504		889	
11	M	460		840	
12	F	504		630	
13	M	685		756	
Mean		551		880	

on Benemid rose to 825 mg., and on G.28 315 400 mg. daily to 880 mg. and on G.28 315 800 mg. daily to 1,042 mg.

Table II shows that the effect on the serum uric acid levels was the opposite to the effect on the uricosuria. In all twelve cases the serum uric acid was markedly reduced and in the six which were also controlled against Benemid the fall was seen to be greater with G.28 315. The mean serum uric acid value of all cases was 7.8 mg. per cent. in the control period, and dropped to 5.2 mg. per cent. on Benemid and to 4 mg. per cent. on G.28 315.

It was thought that intermittent administration of G.28 315, as practised with cincophen, might be more economical and safer than continuous administration. The possibility of using G.28 315 in this way was suggested by the typical charts of greatest excretion during the first 3 days of administration (Fig. 2, opposite).

TABLE II

LEVELS OF SERUM URIC ACID (mg./100 ml. serum) DURING TREATMENT WITH BENEMID OR G.28 315

Patient No.	Sex	Control	Treatment	
			Benemid	G.28 315
1	F	8.0	5.1	2.9
2	M	6.5	4.6	3.4
3	M	9.5	6.3	4.7
4	M	6.2	5.3	4.4
5	M	10.1	—	4.8
6	M	—	—	—
7	M	8.0	4.6	3.8
8	F	7.6	—	5.7
9	M	8.3	—	4.2
10	M	8.8	—	2.8
11	M	7.7	—	5.0
12	F	5.1	—	2.3
Mean		7.8	5.2	4.0

Ten patients were therefore given 400 mg. G.28 315 daily for a week, and then, after a 4-day rest, they were given the same dose of G.28 315 for 3 days followed by a further rest period of 4 days. The average uric acid excretion for the 2 weeks was then compared. The average excretion for the control week was 4,296 mg., for continuous treatment 6,571 mg., and for intermittent treatment 5,787 mg. The disadvantage of intermittent administration was illustrated by the serum uric acid levels; the average value after the use of G.28 315 rose from 3.4 to 8.3 mg. per cent. at the end of the 4-day rest period.

The patients treated with G.28 315 have now been on continuous treatment for from 3 to 8 months. Table III shows that there is no significant falling off in the effect of the drug on uric acid excretion or on the serum uric acid levels. The mean excretion dropped only from 841 to 828 mg. (control 551 mg.) and the serum uric acid rose only from 4.5 to 4.8 mg. per cent. (control 7.8 mg. per cent.).

There have been no toxic symptoms of any kind so far in this group of cases. The white blood counts showed only a slight fall which was not

TABLE III

EFFECTS OF PROLONGED TREATMENT WITH G.28 315

Patient No.	After 1 Week's Treatment		Duration of Treatment (wks)	After Prolonged Treatment	
	Uric Acid Excretion (mg./24 hrs)	Serum Uric Acid (mg./100 ml.)		Uric Acid Excretion (mg./24 hrs)	Serum Uric Acid (mg./100 ml.)
1	744	3.2	12	760	3.9
2	706	3.2	12	759	3.5
3	780	5.2	8	723	5.2
4	1,050	4.6	14	965	4.8
5	1,013	5.2	6	1,154	5.6
11	840	5.0	14	500	4.8
12	—	2.3	4	—	3.0
13	—	7.0	4	—	6.0
14	757	5.1	10	935	6.5
Mean	841	4.5	9	828	4.8

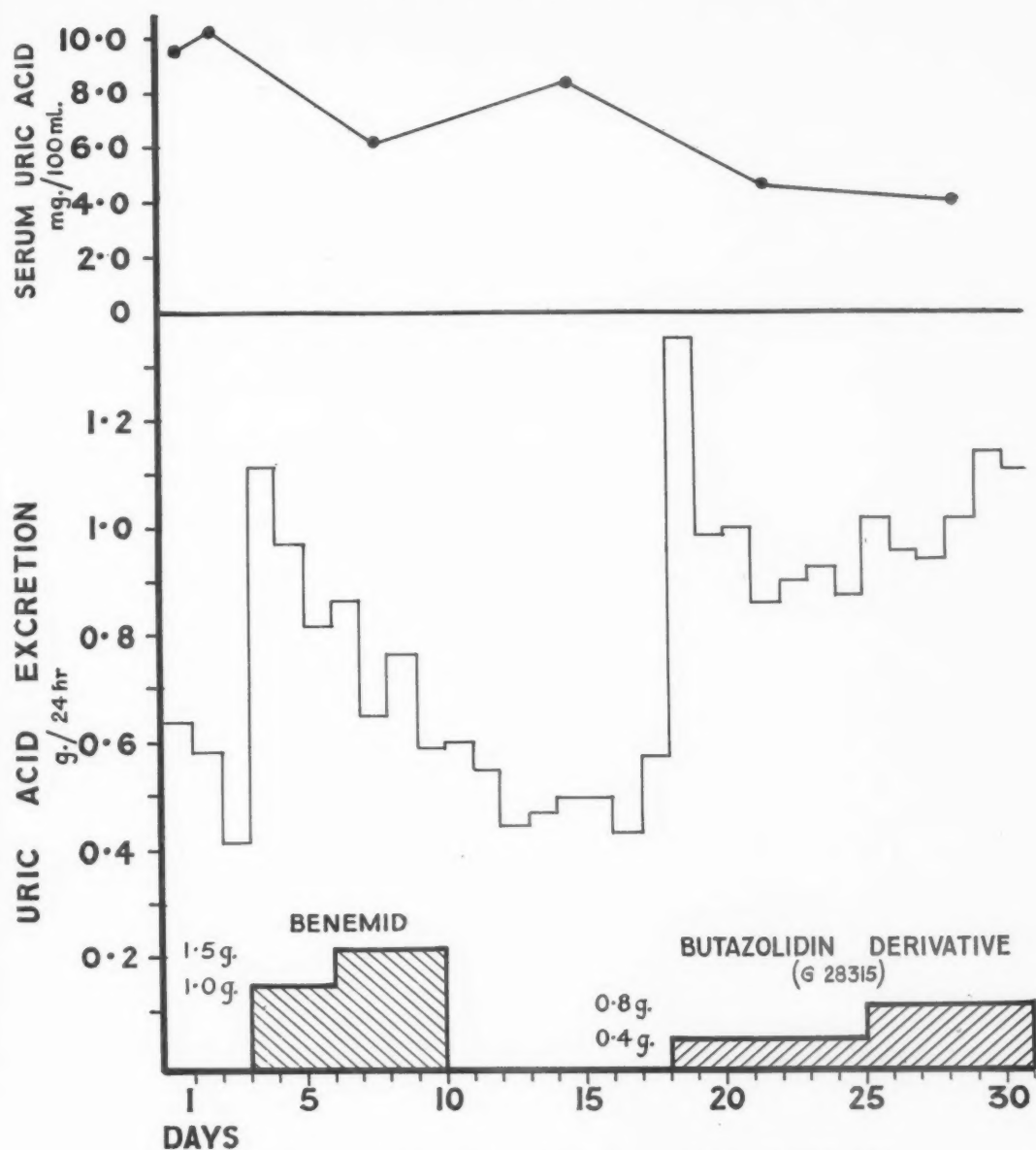


Fig. 2.—Patient 3, a man aged 44, with gout, showing response to Benemid and G.28 315.

progressive, and the percentage of granulocytes did not decrease.

Kersley and others (1951) and Gutman and Yü (1952) noticed that four out of eight cases treated with Benemid developed an acute attack of gout shortly after commencing the drug. Gutman (1957) found no tendency for G.25 671 or G.28 315 to provoke attacks, but Ogryzlo and Harrison (1957) remarked that six out of 25 cases receiving G.25 671 had acute episodes within the first 6 weeks. In the

present series of cases treated with G.28 315, nine out of thirteen developed acute episodes within the first 6 weeks of treatment in spite of a maintenance dosage of colchicine. In one case it was the worst attack he had ever experienced and in the remainder the average interval between commencing treatment and the onset of an attack was shorter than the average intervals during the past 2 years. After this period of 6 weeks, however, attacks became less frequent and also less severe.



In every case the episode was terminated rapidly by the use of phenylbutazone 600 mg. daily for 2 days, marked improvement being seen within 12 hours, even after colchicine had failed (Fig. 3). Even during this 6 weeks initial treatment several patients stated that chronic swelling was disappearing and one woman was able to wear her ring for the first time for 3 years.

Pascale, Dubin, and Hoffman (1952) found that in three cases 5 g. salicylate held up the fall in plasma uric acid usually obtained with Benemid. Yü, Sirota, and Gutman (1953) found that in four cases receiving 1 g. Benemid there was a slight depression

of uric acid excretion on adding 600 mg. phenylbutazone during the first 2 days only, but the result of this addition was rather erratic. Ogryzlo and Harrison (1957) stated that salicylates had some blocking action on the uricosuria of G.25 671 and G.28 315, but that G.25 671 had no such effect on the excretion occasioned by Benemid.

As aspirin is so often given (or taken without permission) in gout, nine patients were stabilized on 400 mg. G.28 315 and 3.5 g. aspirin was given in addition. The fall in excretion of uric acid was startling; in eight it fell well below the control value and a similar sudden rise occurred in the serum uric

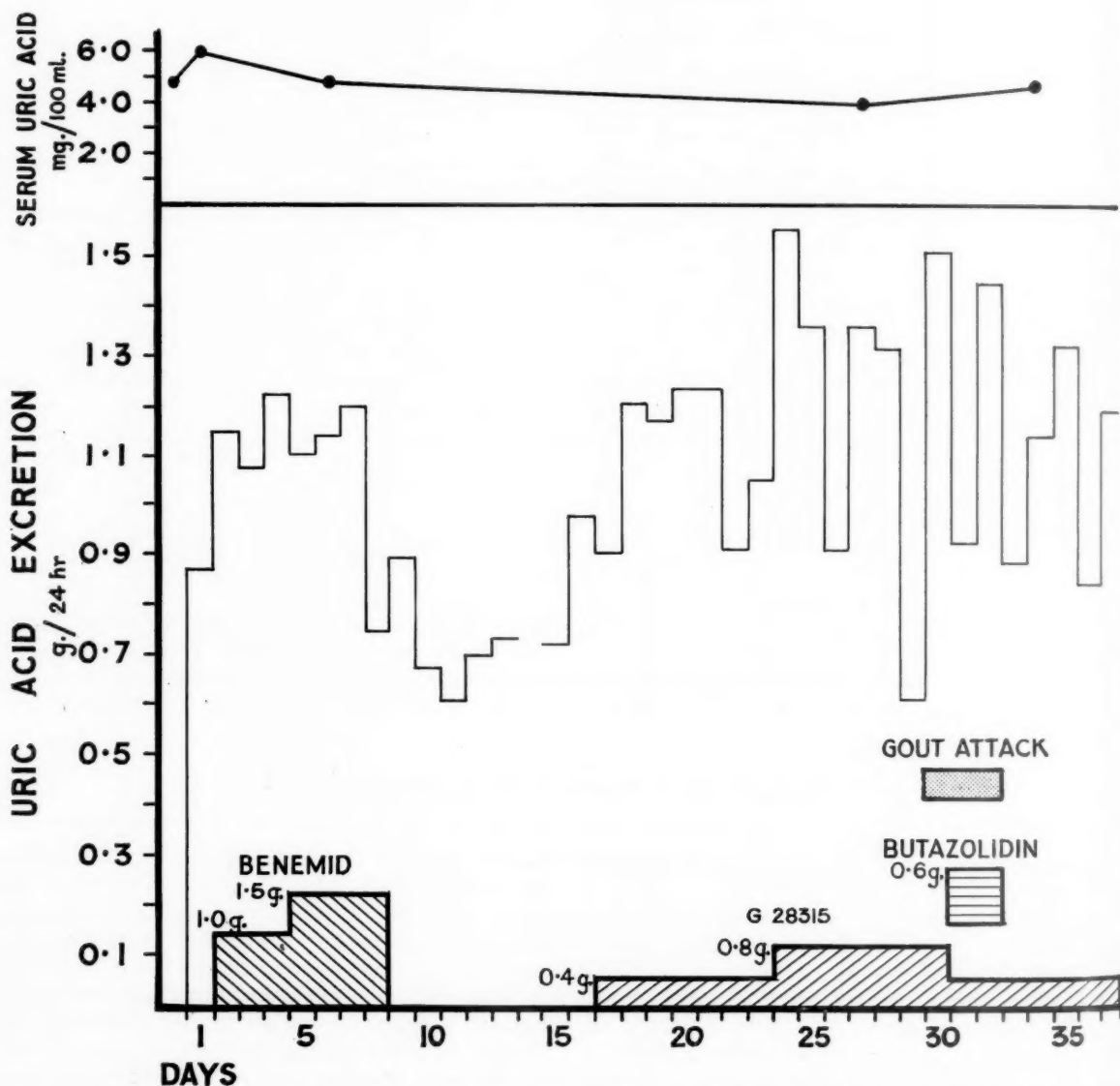


Fig. 3.—Patient 4, a man aged 41, with gout, showing response to Benemid and G.28 315, and added Butazolidin during an acute attack

TABLE IV  
INHIBITORY EFFECT OF ASPIRIN UPON URICOSURIA INDUCED BY G.28 315

Patient No.	Sex	Uric Acid Excretion (mg./24 hrs)			Serum Uric Acid (mg./100 ml.)		
		Control	G.28 (0.4 g./24 hrs)	G.28 + Aspirin 3.5 g.	Control	G.28 (0.4 g./24 hrs)	G.28 + Aspirin 3.5 g.
1	F	406	800	241	8.8	3.9	11.4
2	M	524	869	540	4.2	3.5	4.4
3	M	521	730	303	8.6	5.2	7.3
5	M	860	1,197	635	9.9	5.6	—
7	M	594	883	373	8.6	5.4	8.2
8	F	435	794	255	7.4	5.7	10.4
9	M	791	1,367	531	8.3	4.2	10.6
10	M	463	1,061	307	6.3	3.3	9.4
14	M	588	820	426	6.9	6.5	9.8
Mean		576	947	401	7.7	4.8	8.8

acid (Table IV). The mean values for daily excretion were control 576 mg., on G.28 315 947 mg. and on G.28 315 plus 3.5 g. aspirin 401 mg. The corresponding serum uric acid means were 7.7, 4.8, and 8.8 mg. per cent.

In two out of three cases given only 0.7 g. aspirin together with G.28, the uric acid excretion fell to the control value, about a 25 per cent. decrease, but in the third patient there was no significant change. Three cases were given 120 mg. caffeine with their aspirin, and it was of interest to note that this increased the daily uric acid excretion by approximately 200 mg. Adding 3.5 g. glycine to the aspirin had a very similar effect.

During the later stages of the trial, we were asked to compare the results obtained with G.28 with those obtained with Longacid (p-carboxybenzalsulphodiethylamide), a drug of the Benemid type. Eleven patients were tested for a period of 1 to 12 weeks on this drug in a dosage of 1 to 2 g. daily. All showed an increase in uric acid excretion and all but one a reduction in the plasma uric acid level, but in only three was the benefit comparable with that obtained with 400 mg. G.28. There were no toxic sequelae, but four patients complained, without questioning and for no apparent reason, of feeling very tired while taking the drug. All but one were pleased to return to G.28 medication.

In only two patients was renal function impaired, though two others had some transitory pain in the loins and red cells and crystals in the urine during the first 2 days of G.28 315 administration.

One patient aged 46 had a blood pressure of 230/120, 1.8 g. albumin in the urine, but no red cells, and a blood urea of 60 mg. per cent. on admission. During treatment the blood pressure gradually dropped to 170/100, the albumin decreased to 1.1 g., and the blood urea to 48 mg. per cent. In this patient the control average daily output of uric acid was 570 mg., and this rose to 800 on Benemid administration and to 1,000 on 400 mg. G.28 315

daily. The serum uric acid fell from 10.3 to 8.6 mg. per cent. on Benemid and to 6.9 mg. per cent. on G.28 315.

A second patient aged 52 had a blood pressure of 165/110, 0.9 g. albumin in the urine, and a blood urea of 45 mg. per cent. He developed a slight headache during the first few days of treatment but had no other untoward symptoms; the blood pressure tended to drop rather than rise and the urinary findings did not deteriorate. The control average daily output of uric acid was 550 mg. rising to 900 on Benemid and to 880 on 400 mg. G.28 315 daily. The serum uric acid fell from 7.8 to 6.5 mg. per cent. on Benemid and to 5 mg. per cent. on G.28 315.

This suggests that, except when there is advanced renal failure, it is safe and useful to administer 1 g. Benemid or 400 mg. G.28 315 daily, provided plenty of fluids are given, the urine is not acid, and the patient is carefully observed.

### Summary

(1) In fifteen patients with typical gout the effect of G.28 315 on the clinical condition, uric acid excretion, and serum uric acid levels has been investigated.

(2) In two patients with abnormal renal function who are considered separately, the response was very satisfactory.

(3) In the remaining thirteen patients, the average daily excretion of uric acid rose from 551 to 880 mg. on a dosage of 400 mg. G.28 315 daily, and to 1,042 mg. in five cases on a dosage of 800 mg. G.28 315. The average serum uric acid fell from 7.8 to 4 mg. per cent.

(4) In five cases, the effect of 800 mg. G.28 315 was found to be significantly higher than that of 1 to 1.5 g. Benemid, and the average drop in the serum uric acid level was greater (from 7.8 to 4 mg. instead of to 5.2 mg. per cent.).

(5) Intermittent administration for 3 days per

week did not maintain the low serum uric acid level.

(6) Continuous treatment for 3 to 8 months produced no toxic effects. There was an increased attack rate for the first 6 weeks and thereafter attacks became very infrequent and mild and regression of long-standing swelling was produced. Phenylbutazone terminated attacks at once in all cases.

(7) The addition of 3.5 g. aspirin to the G.28 315 medication completely reversed its effect, causing a fall in uric acid excretion below even the control value, and also a maximal rise in the serum uric acid level; an appreciable fall in uric acid excretion was noted in two of three patients on the addition of only 0.7 g. aspirin.

(8) The results of the use of 1 to 2 g. Longacid were compared in eleven cases. In all, there was an increased excretion of uric acid and in ten a drop in the plasma uric acid level; in only three, however, were the beneficial effects comparable with those obtained with 400 mg. G.28 315.

It seems probable that G.28 315 may be of considerable therapeutic value in the interval treatment of gout, in a dosage of 400-800 mg. daily. It appears so far to be completely non-toxic and be more efficacious in lowering the serum uric acid level and increasing the uric acid excretion than the usually prescribed dosage of Benemid.

We should like to express our thanks to Dr. W. S. Stoddart of Geigy Pharmaceutical Company for co-operation and for the supply of the G.28 315 used in this clinical trial, and to Ward, Blenkinsop and Company Ltd. for the supply of Longacid.

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#### Valeur des agents uricosuriques et en particulier du G.28 315 dans la goutte

##### RÉSUMÉ

(1) On a étudié l'effet du G.28 315 sur l'état clinique, l'élimination d'acide urique et le taux sérique d'acide urique chez 15 malades atteints de goutte typique.

(2) Chez deux malades, dont la fonction rénale était anormale et qu'on considère pour cela séparément, la réponse était très satisfaisante.

(3) Chez les 13 autres malades, l'élimination moyenne par jour d'acide urique monta de 551 à 880 mg. avec une

dose de 400 mg. de G.28 315 par jour, et dans 5 cas, une dose de 800 mg. éleva l'uricosurie à 1.042 mg. Le taux moyen d'acide urique sanguin tomba de 7,8 mg. à 4 mg. pour cent.

(4) Dans cinq cas l'effet de 800 mg. de G.28 315 fut nettement supérieur à celui de 1 à 1,5 g. de Bénémide, et la chute moyenne du taux sanguin d'acide urique fut plus accentuée (de 7,8 mg. à 4 mg. au lieu de 5,2 mg. pour cent).

(5) Un traitement intermittent de 3 jours par semaine ne suffit pas pour maintenir le taux bas d'acide urique sanguin.

(6) Un traitement continu pendant 3 à 8 mois ne produisit pas d'effets toxiques. Le nombre d'attaques augmenta pendant les premières 6 semaines, après quoi ils devinrent bénins et peu fréquents et on observa une régression des tophus anciens. La phénylbutazone terminait toujours les attaques très rapidement.

(7) Quand on ajoutait 3,5 g. d'aspirine à la médication par le G.28 315, l'effet de celui-ci était renversé: l'uricosurie tombait en dessous du chiffre de contrôle et l'uricémie montait à son maximum. Chez deux sur trois malades on obtint une chute appréciable de l'uricosurie avec 0,7 g. seulement d'aspirine.

(8) Chez 11 malades on compara les résultats obtenus avec l'emploi de 1 à 2 g. de Longacid. Chez tous l'uricosurie augmenta et chez dix l'uricémie diminua, mais chez trois seulement l'effet favorable du Longacid fut comparable à celui de 400 mg. de G.28 315.

Il semble que la valeur du G.28 315 dans le traitement de la goutte entre les attaques, en doses de 400 à 800 mg. par jour, est considérable. Autant qu'on sache, il est tout à fait atoxique et plus efficace que le Bénémide en doses habituelles pour faire diminuer le taux sérique d'acide urique et augmenter son excrétion urinaire.

#### Valor de los agentes uricosúricos y en particular del G.28 315 en la gota

##### SUMARIO

(1) Se estudió el efecto del G.28 315 sobre el estado clínico, la eliminación de ácido úrico y la tasa sérica de ácido úrico en quince enfermos con gota típica.

(2) En dos enfermos, considerados separadamente por acusar la función renal anormal, la respuesta fué muy satisfactoria.

(3) En los demás trece enfermos, la eliminación diaria media de ácido úrico subió de 551 a 880 mg. con una dosis diaria de 400 mg. de G.28 315 y, en cinco casos, una dosis de 800 mg. hizo subir la uricosuria a 1.042 mg. El ácido úrico sérico bajó de 7,8 mg. a 4 mg. por ciento.

(4) En cinco casos el efecto de 800 mg. de G.28 315 fué netamente superior al efecto de 1 a 1,5 gramos de Benemid y la baja de la uricemia fué más acusada (de 7,8 a 4 mg. en vez de 5,2 mg. por ciento).

(5) Un tratamiento intermitente de 3 días por semana no basta para mantener una cifra baja de ácido úrico en el suero.

(6) Un tratamiento continuo de 3 a 8 meses no produjo efectos tóxicos. El número de ataques aumentó durante las primeras 6 semanas, pero luego estos ataques se volvieron poco frecuentes y benignos y una regresión de tofos antiguos fué observada. La fenilbutazona siempre cortaba los ataques.

(7) Al añadir 3,5 g. de aspirina a la medicación con el

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G.28 315, se obtenía un efecto inverso: la uricosuria caía debajo la cifra de control y la uricemia alcanzaba lo máximo. En dos de tres enfermos hubo una baja apreciable de la uricosuria con sólo 0,7 g. de aspirina.

(8) En 11 enfermos se compararon los resultados obtenidos con 1 a 2 g. de Longacid. La uricosuria aumentó en todos y la uricemia disminuyó en diez casos, pero en tres casos solamente el efecto favorable de

Longacid se pudo comparar al obtenido con 400 mg. de G.28 315.

El valor del G.28 315 en el tratamiento de la gota entre los ataques, en dosis diarias de 400 a 800 mg., parece considerable. A lo que se sabe, este producto es enteramente atóxico y más eficaz que el Benemid en dosis habituales para hacer bajar la uricemia y subir la uricosuria.



## INVOLVEMENT OF THE NERVOUS SYSTEM IN REITER'S SYNDROME

BY

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Reiter's syndrome is a condition of unknown aetiology, generally thought to be of infective origin. It occurs mainly in young men and is characterized by urethritis, arthritis, and conjunctivitis. Less common findings include ankylosing spondylitis, iritis, balanitis, keratoderma blennorrhagica and other skin lesions, stomatitis, and inflammations of the tendons and fasciae. According to the literature neurological complications seem to be extremely rare, and for this reason the following case is presented.

### Case Report

A labourer, aged 29 years, had suffered from recurrent attacks of urethritis, acute polyarthritis, and conjunctivitis since he was 17 years old. Between attacks he felt perfectly well and was able to do a full day's work. In May, 1950, he attended St. Mary's Hospital for the first time, with non-specific urethritis (N.S.U.): 8 days later, arthritis, circinate balanitis, and conjunctivitis developed, his fourth attack of Reiter's syndrome. He was admitted to hospital and the symptoms subsided gradually during the next 2 months, when he left hospital against advice. A few days later he developed acute urinary retention, double vision, nausea, dizziness, and an acute pain in the back of the neck. He also noticed a tickling sensation on the right side of his face and, some days later, a heaviness in both legs. Double vision and dizziness improved after 3 weeks and the difficulty of micturition after 6 weeks, and the rest of the neurological symptoms disappeared within the next 3 months.

He remained well until December, 1951, when he contracted gonorrhoea which was followed by persistent N.S.U. A week later arthritis and conjunctivitis appeared, together with double vision, dizziness, and vomiting. The locomotor and neurological symptoms again subsided gradually and the patient felt fit 5 months later when his convalescence was temporarily interrupted by thrombophlebitis of the left calf veins. In August, 1953, a further attack of urethritis followed a venereal risk and this was, in turn, followed within a week by arthritis, conjunctivitis, pain over the sacroiliac joints, thrombophlebitis of the calf veins on the right side, and keratoderma blennorrhagica. This attack was not

accompanied by a recurrence of neurological symptoms and he made a good recovery within 3 months.

He remained well until March, 1955, when dizziness, diplopia, and heaviness of the legs recurred. This was followed, 2 weeks later, by slight N.S.U., arthritis, and conjunctivitis, and at the same time a rash with the characteristics of erythema multiforme of the iris type appeared on the forearms and legs. According to the patient, the most unusual feature of this latest episode was the fact that there had been no sexual intercourse for at least 3 months preceding its onset, unlike the earlier attacks. Symptomatic recovery was rapid both as regards locomotor and neurological symptoms, and he was discharged from hospital in May, 1955. He has not attended since that time.

The main clinical events are shown chronologically in the Figure (opposite).

*Personal History.*—No major or relevant illness.

*Family History.*—Negative for rheumatic and neurological disorders.

*Examination.*—In the course of the seven attacks of Reiter's syndrome, most of the joints of the lower limbs were involved, but only the left wrist and right shoulder of the upper limbs. Of the central joints, the sacro-iliac articulations were markedly tender and painful in the later attacks; the rest of the spine was symptom free. Between attacks, the previously-affected peripheral joints were clinically and functionally normal. Plantar fasciitis with painful heels was present with every attack. Bilateral angular conjunctivitis was seen early with every episode of arthritis and lasted from 3 days to 2 weeks. Circinate balanitis developed for the first time during the fourth attack.

*Nervous System (January 2, 1952).*—The optic disks were normal; the visual acuity was 6/6 in the right eye and 6/12 in the left; the fields of vision were full. There was slight ptosis on the left side, and a sustained fine rapid nystagmus with a rotary element developed in both eyes on lateral conjugate deviation and was more marked on looking to the left.

There was a VIth nerve palsy on the left side and hyperalgesia over the right side of the face, including all three divisions of the fifth cranial nerve, and hyperaesthesia over the 2nd and 3rd divisions. Corneal

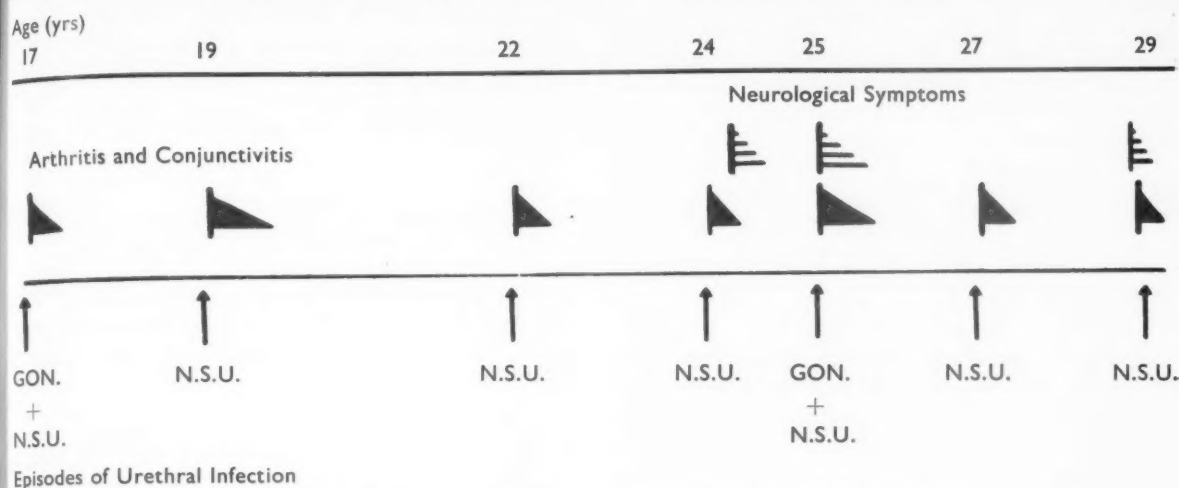


Figure.—Diagram showing clinical symptoms during successive episodes of urethral infection.

reflexes and motor function of the nerve were normal. There were no other sensory changes. There was right lower facial weakness; the other cranial nerves were normal.

The left arm fell away and was more easily displaced than its fellow and there was clumsiness in the performance of rapid alternating movements of the left forearm. The motor functions were otherwise normal.

The arm reflexes were normal; knee jerks pathologically brisk on both sides; ankle jerks normal; plantar responses flexor; abdominal reflexes absent.

In the next few days there was some extension of the hyperalgesia into the territory of the right cervical plexus and marked increase of the ptosis on the left side.

(August 7, 1953) The neurological symptoms and signs were less marked, except for the left external rectus paralysis which remained unchanged. The reflexes of the lower limbs were now sluggish.

(March 7, 1955) The only abnormal neurological sign was the left external rectus paralysis.

The patient was mentally normal throughout his illness.

**Laboratory Investigations.**—Haemoglobin 13.3 to 14.8 g. per 100 ml. (several estimations); mean corpuscular diameter  $7.2\mu$ ; total white count showed a variable slight neutrophil leucocytosis during the acute phases of arthritis.

The Wassermann, Kahn, and gonococcal complement-fixation tests were performed during every attack with negative results.

The erythrocyte sedimentation rate (Westergren) was raised with every arthritic episode, the highest reading being 106 mm./hr.

The cerebrospinal fluid (January 25, 1952) was clear and colourless with normal dynamics; no cells were seen; protein 15 mg. per 100 ml.; Pandy negative; Lange 0000000000; Wassermann negative. A further sample collected on March 10, 1952 gave identical results.

Total serum protein (January 3, 1952) was 7.4 g. per 100 ml.; albumin 4.7 g. per 100 ml.; globulin 2.7 g. per 100 ml. Similar results were obtained during the attacks in 1953 and 1955.

The Rose-Waaler differential agglutination test (D.A.T.) was negative on January 9, 1952, and August 27, 1953. C-reactive protein was negative.

Catheter specimen urine showed pus cells repeatedly and occasional red blood cells. Cultures yielded *E. coli* and enterococci.

The urethral discharge was sterile, except on the two occasions in 1943 and 1951, when gonococci were present. Prostatic fluid obtained by massage in April, 1955, showed from twenty to thirty pus cells per high-power field.

Investigations for pleuro-pneumonia-like organisms (PPLO) were undertaken by Dr. Klieneberger-Nobel at the Lister Institute, London, on material from the urethra, conjunctivae, and synovial fluid from an affected knee joint, with negative results; the serum complement-fixation test against PPLO was also negative (April 14, 1955).

**Radiology.**—X-rays of the chest, skull, hands, and cervical, dorsal, and lumbar spine were normal. The feet showed bilateral calcaneal spurs and some periosteal new bone formation at the base of the right medial malleolus. Two small calcified opacities were noted behind the lower end of the right tibia and were thought to be phleboliths. The sacro-iliac joints showed sub-articular sclerosis (April 4, 1955).

**Treatment and Progress.**—The initial non-specific urethral infections were treated with a variety of antibiotics (aureomycin, terramycin, sulphadiazine, and streptomycin) with little improvement of the urethritis and without effect on the development of arthritis and other complications. Gonorrhoea was treated with procaine penicillin injections, which apparently cleared the gonococcus, but did not prevent the emergence of Reiter's syndrome. During the attacks of arthritis, the

main lines of treatment were salicylates in full doses and artificial fever therapy induced by intravenous injection of typhoid vaccine (T.A.B.) with temporary improvement in the affected joints. ACTH 25 mg. daily, given by slow intravenous drip from April 16, 1952, resulted in an immediate response of the affected joints, but without influencing the neurological signs and symptoms. The neurological disorder appeared at its most severe and widespread a few days after its onset and became less marked on the occasion of the recurrences over the next 5 years. No new neurological features occurred in the later attacks.

### Discussion

In view of the established relationship of Behcet's syndrome with neurological involvement (Knapp, 1941; Berlin, 1944; Phillips and Scott, 1955; Pallis and Fudge, 1956; Evans, Pallis, and Spillane, 1957), this diagnosis was carefully considered, especially as Behcet's syndrome bears a superficial likeness to Reiter's syndrome. However, circinate balanitis and keratoderma blennorrhagica, which were present in our case, are not found in Behcet's syndrome, nor is the relationship of the recurrent attacks with venereal urethritis. Arthritis is uncommon in Behcet's syndrome (*Lancet*, 1958) and does not form a dominant and integral part of the illness as in Reiter's syndrome and in our patient.

A diagnosis of multiple sclerosis precipitated by genital infection seems unlikely, in view of the abrupt onset of a number of neurological signs and symptoms, which reached their greatest extent and severity early in the attack and from then onwards began to improve; furthermore, no new neurological lesions made their appearance after the first episode.

The possibility of a chance association of Reiter's syndrome with a neurological disorder of unknown aetiology cannot be disproved in this case, but a more direct relationship is favoured by the appearance of neurological symptoms soon after the onset of an attack of the syndrome and the subsequent lighting up of the nervous disorder by two further attacks.

Anatomically, the neurological signs and symptoms in this young man are thought to be due to widespread involvement of the brain stem, but perhaps significantly, they cannot easily be fitted into any category of known primary nervous disease.

### Summary

A case of recurrent Reiter's syndrome with clinical involvement of the central nervous system is reported. The neurological signs and symptoms closely follow the activity of the syndrome and it is suggested that the association is not merely fortuitous.

I am grateful to Dr. G. L. M. McElligott, Dr. H. Edwards and Mr. A. J. King for their helpful criticism and advice. This work was carried out under the aegis of the Medical Research Council Working Party on Non-Specific Urethritis, with the aid of a grant from the U.S. Public Health Service.

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### Implication du système nerveux dans le syndrome de Reiter

#### RÉSUMÉ

On rapporte un cas de syndrome de Reiter recurrent avec implication clinique du système nerveux central. Les signes et les symptômes neurologiques accompagnent l'activité du syndrome de très près et on suggère que cette association n'est pas entièrement fortuite.

### Implicación del sistema nervioso en el síndrome de Reiter

#### SUMARIO

Se relata un caso de síndrome de Reiter recurrente con implicación clínica del sistema nervioso central. Los signos y los síntomas neurológicos siguen de muy cerca la actividad del síndrome y se sugiere que esta asociación no es enteramente fortuita.

## HEBERDEN SOCIETY

### Heberden Round

Prof. J. Goslings conducted the annual Heberden Round at the University Hospital, Leyden, on April 25, 1958. His theme was the association of pericarditis and rheumatoid arthritis. Thirteen patients were presented, three of whom had come to autopsy. Most of the patients had severe active rheumatoid arthritis, and some had other visceral involvement. Several showed the lupus erythematosus cell phenomenon. In four patients, however, pericarditis had been recognized where the duration of rheumatoid disease was less than 18 months. The clinical recognition of pericarditis was sometimes difficult, as physical signs might be transient and the electrocardiogram negative in cases showing pericarditis at autopsy. Prof. Goslings thought that the difficulty of detecting pericarditis during life might explain some of the difference between the reported prevalence of pericarditis in patients with rheumatoid arthritis and that seen in autopsy series.

### Joint Meeting of the Heberden Society and the Dutch Society of Rheumatologists

At a meeting held on April 26, 1958, the following papers were given:

J. A. SZIRMAI (Leyden): **Quantitative Aspects of the Metachromatic Reaction.**—The interaction between cationic dyes and anionic polysaccharides was characterized by two interdependent reactions: metachromasia and the formation of relatively insoluble precipitates. The stoichiometry of the second type of reaction was described and it was shown that both the carboxyl and sulphate ester sites participated in this reaction.

The quantitative aspects of the interaction between cationic dyes and tissue components had been studied, using rooster comb and cartilage. The amount of the dye bound in the polyacid-dye complex could be determined quantitatively from the optical density of a dye solution after immersion of a piece of tissue in it. Various factors influencing this reaction, such as the tissue-dye ratio, the dyebath concentration, the thickness of the tissue section, and mechanical agitation, had been studied. Under standard conditions the amount of dye bound by a given tissue depended only on the pH of the dyebath. It was suggested that electrostatic interaction between the cationic dye and the anionic sites of the tissue was primarily responsible for the dyebinding, and that the value obtained was a measure of the free anionic sites in a tissue.

The quantitative nature of this reaction had been further studied by comparing the mucopolysaccharide content of the tissues with their dyebinding properties.

This had been done on the fresh tissue before and after water extraction and on the water extract. The molar ratio of dye bound to anionic sites of the polysaccharides varied between 1.1:1 and 1.8:1, with the exception of the rooster comb extract where it was 1:1. This indicated that, except in the latter case, in addition to the acid groups of polysaccharides other anionic sites were also responsible for dye uptake.

The results showed that, in spite of the stoichiometric character of the interaction between cationic dyes and acid mucopolysaccharides, this method could not be used for the quantitative determination of mucopolysaccharides in tissues, as it measured the total number of free anionic sites and thus gave only a rough approximation of the amount of acid mucopolysaccharides present. In many cases such an approximate measure could be useful; this was shown by the close correlation between the metachromatic staining and the dye uptake of the tissues studied. The quantitative nature of this reaction suggested its usefulness for direct microspectrophotometric measurements of the metachromasia in tissue sections.

L. T. F. L. STUBBE (Leyden): **Occult Faecal Loss of Blood Caused by the Use of Acetylsalicylic Acid.**—Occult loss of blood in the faeces was proved to occur in about 70 per cent. of the 180 persons to whom acetylsalicylic acid in the form of tablets had been administered with milk or water shortly after a meal. A meat-free diet was prescribed and the patient was not allowed to brush his teeth. As a rule the meat-free diet was prescribed after the patient had been taking acetylsalicylic acid for 14 days.

The first three lots of faeces after the diet had been started were not used. Only positive or negative reactions found in three successive lots of faeces were recorded. The concentration of the benzidine solution used was about 0.75 per cent. For quantitation, five different grades were established (from negative to strongly positive) according to the speed at which the colour of the reaction developed. When no acetylsalicylic acid was taken, the benzidine reaction was always negative. It was possible to demonstrate spectroscopically and spectrophotometrically that a positive benzidine reaction after the taking of acetylsalicylic acid was due to the presence of blood.

Results obtained in the 140 patients admitted to the wards of the Rheumatology Department who were treated with acetylsalicylic acid were entirely comparable with those found in the control group consisting of forty healthy volunteers.

It was possible to prove conclusively that the acetylsalicylic acid was the cause of this loss of blood as this phenomenon appeared to be reproducible. The quantity of acetylsalicylic acid administered did not have a



conspicuous influence on the occurrence or severity of the blood loss. The most common doses were 1,500 and 3,000 mg. per day.

Identical results were obtained when acetylsalicylic acid in powder form suspended in water was administered to a small group as when the same persons were given this drug as tablets. Of the ten patients who were examined after they had taken coated tablets of acetylsalicylic acid, only two showed a negative benzidine reaction. After administration of sodium salicylate tablets the benzidine reaction was always negative.

In a number of persons it was shown, on the basis of the strength of the benzidine reaction, that the quantity of blood lost when acetylsalicylic acid was taken might not always be negligible. It was found that when 4 ml. blood was administered orally during a day (ten times 0.4 ml.) there was a strongly positive benzidine reaction. This suggests that a patient with a strongly positive reaction may lose about  $30 \times 4 \text{ ml.} = 120 \text{ ml.}$  blood per month, which may be comparable with the average menstrual loss, stated to be 40 ml.

**E. KRUYFF (Wassenaar): Incidence of Leukaemia in Patients with Ankylosing Spondylitis treated with  $\alpha$  Rays.**—In a group of 1,996 Dutch patients with ankylosing spondylitis treated with radiotherapy, in whom a follow-up rate of over 90 per cent. had been achieved, there had been 256 deaths, 25 of which were due to leukaemia or aplastic anaemia, thus confirming the enhanced incidence of leukaemia after radiotherapy (Van Swaay, 1950). These figures were compared with those obtained for England and Wales by the Medical Research Council, but the statistics were not strictly comparable because of differences in dosage, age, and completeness of follow-up (46 per cent. in the M.R.C. series). Several instances of leukaemia in patients treated with deep  $\alpha$  rays for conditions other than ankylosing spondylitis were reported. The incidence of leukaemia was steadily rising in the Dutch population as a whole.

**S. A. DEN OUDSTEN AND B. SPEYER (Rotterdam): Spontaneous Fractures in Rheumatoid Arthritis.**—During the last 10 years 1,104 patients with "definite" rheumatoid arthritis (American Rheumatism Association criteria) were seen in South Rotterdam, which has a population of 235,000; 206 of these could be placed in Stages III and IV of the A.R.A. classification. Population studies indicated that 90 per cent. of all cases of rheumatoid arthritis were registered by the arthritis service. Of these 206 severer cases, 157 were available for a study of the prevalence of spontaneous fractures.

Nine patients showed non-spinal spontaneous fractures, seven of them in the femoral neck. The patients ranged in age from 25-85 years, 105 being over 60. In a control group of 105 non-rheumatoid patients over 60 years of age and comparable to the older rheumatoid patients as regards sex, age, and physical incapacity, spontaneous fractures were found six times. The difference between these groups was not significant. The incidence of non-spinal spontaneous fractures was significantly greater in invalids than in non-invalids and

they occurred more frequently in women than in men.

Spinal fractures were found in four patients in the rheumatoid group and in four out of a second control group of 157 patients without rheumatoid arthritis. In women spinal osteoporosis was found significantly more often in the rheumatoid group than in the control group, but the possibility that this difference was due to the degree of incapacity could not be excluded.

Spontaneous fractures were seen in two out of fourteen patients who had been on long-term corticosteroid therapy, and in eleven of 143 patients who had never received these hormones. The difference was not statistically significant.

**H. A. VALKENBURG AND C. A. DE MOS (Leyden): Latex-Fixation Test as a Diagnostic Aid.**—The latex-fixation test (Singer and Plotz, 1956) was reviewed and slight modifications introduced. Instead of borate-buffer, glycine-buffer (pH 8.2) was used, and after incubation in a waterbath at 56° C. the tubes were allowed to stay at room temperature for 20 to 24 hrs. Incubation at 37° C. was omitted, as false positive reactions resulted. Examined in this way, 110 of 120 serum samples obtained from 54 patients were reproducible within two dilutions. Statistical analysis of the serologic procedure showed the latex test to be a reliable routine test. When exceeding a titre of 1:20, patients were considered to have a positive latex-fixation test. As many sera showed a marked prozone effect, a 1:20 dilution could not be used for a screening procedure. A considerable proportion (about 10 per cent.) of serum samples in the non-rheumatoid groups which exhibited this prozone phenomenon were called weakly positive. Varying proportions of gamma globulin and/or latex-particles were shown to be only partly responsible for these weak reactions.

Serum samples from 1,023 patients and control subjects were investigated, American Rheumatism Association criteria being used for the rheumatoid arthritis group of 337 patients. Of 238 patients with "definite" rheumatoid arthritis, 207 (87 per cent.) showed positive reactions. 53 patients suffering from "definite" rheumatoid arthritis complicated by a positive L.E.-cell phenomenon exhibited positive reactions in 90.6 per cent. Only four of sixteen patients with "definite" rheumatoid arthritis complicated by psoriasis were positive. 300 (83.3 per cent.) of 360 patients with non-rheumatoid disease gave negative latex-fixation tests. This group included 23 patients suffering from systemic lupus erythematosus and five with scleroderma; positive reactions were seen in 35 and 80 per cent. respectively. Positive results were found in 11.8 per cent. of a group of 101 patients with non-rheumatic diseases and in 7.6 per cent. of 225 normal subjects. When corrected for weak reactions, the percentages of positive reactions in the "definite" rheumatoid group and the normal control group were 84 and 3.1 per cent. respectively. Taking all non-rheumatoid patients together, 3.6 per cent. gave strong positive reactions. A follow-up investigation would be necessary to determine the possible significance of weak reactions.

W. HJUMANS AND H. R. E. SCHUIT (*Leyden*): **Lupus Erythematosus Cell Phenomenon.**—Lupus erythematosus cells could be found in diseases other than systemic lupus erythematosus, and therefore this phenomenon could not be regarded as absolutely specific. Of a series of 2,000 patients, two hundred were found to be positive, and only one of the positive cases could not be classified as belonging to the group of the so-called collagen diseases. This phenomenon might therefore be used as a tool for further investigation of this group of diseases.

A sound basis for further studies was provided by standardization of the technique, and quantitation of this phenomenon. Positive sera on dilution showed gradually decreasing ability to produce L.E. cells and these were never observed in dilutions greater than 1:32.

In recent years the hypothesis that the L.E. cell is the result of an immunological mechanism had received strong support. Additional data were presented, in accordance with this concept whereby nucleoprotein, or part thereof, but not desoxyribo nucleic acid, could be regarded as antigen and the L.E. cell factor as auto-antibody. It proved possible to absorb L.E. sera with nuclei from different sources as thymocytes and chick erythrocytes in a quantitative way as well as with purified nucleoprotein preparations. The final proof of this concept was still lacking. Apart from a more detailed chemical definition of the active component of the nucleoprotein, it had still to be shown that this component could act as an antigen.

Although it was tempting to ascribe a role in the pathogenesis of some of the collagen diseases to the L.E. cell factor, there was no direct proof of this assumption. There were indications that the presence of this factor should be regarded as an epiphenomenon.

A. VAN DEN HOOFF, W. HJUMANS, AND M. J. W. KASTELEIN (*Leyden*): **Ultrastructure of Streptococcal L-Forms.**—L-forms of Group A beta-haemolytic streptococci were studied under the electron microscope. By making use of the property of these fragile organisms to grow into the agar medium, it was possible to make ultrathin sections of total  $\text{OsO}_4$ -fixed cultures in agar, embedded in methacrylate.

The cultures were found to consist of thin-walled vesicles up to several micra in diameter, each with a distinct outer limiting membrane and a rather irregular wall-structure. Moderately osmophilic granules varying from 300 to 3,000 Å were found embedded in the vesicle walls. In addition "microvesicles" of 100-300 Å were observed in the vesicle walls; all these wall structures were bulging into the interior of the vesicles; only the largest granules (3,000 Å) were bulging outward or lying free.

Each vesicle contained an irregular system of thin membranes attached to the vesicle wall or floating free. Attached to these membranes were granules, a few hundred Å in size, showing marked osmophilia. Transitions between the largest granules and the vesicles were observed.

On the basis of the observations described, a tentative hypothesis concerning the developmental cycle of the

L-forms was put forward. The basic transformation was thought to consist of a vacuolization and swelling of compact full-size granules into vesicles; at the same time, by a budding mechanism, small granules developed in contact with the inside of the vesicular wall. When full-grown, these granules became detached and vacuolized, thus starting a new cycle. Whether the microvesicles played a role in morphogenesis could not be decided. The nature of the intravesicular system of membranes and granules was obscure.

The question was raised whether the structures found were components of the normal bacteria, rendered visible by a partial disintegration effect.

J. M. F. LANDSMEER (*Leyden*): **Functional Anatomy of Finger Movements.**—Contraction of the long tendons of a finger tended to produce a zig-zag deformity of the proximal and middle phalanges. The direction of movement of these phalanges depended on the forces acting on the individual bones, and these forces were related to the distance of the line of pull of the tendons from the centres of rotation of the interphalangeal joints over which they passed. In the normal finger, this zig-zag change was prevented by a system of muscular and ligamentous checks at the metacarpal and interphalangeal joints, but disease of these joints such as occurred in rheumatoid arthritis would displace the line of pull of the tendons, or the site of action of the checking mechanisms, and might accentuate rather than prevent the natural tendency to "zig-zag".

A most enjoyable social programme included a reception by the Burgomaster of Leyden in the historic Lakenhal, a visit to the Bulb Research Institute, and a dinner held under the auspices of the International Study Centre for Rheumatic Diseases, Amsterdam. Dr. J. Van Breemen, Honorary President, and Professor P. Formijne, President of the International Study Centre, Dr. J. J. de Blécourt, on behalf of the Dutch Society of Rheumatologists, and Prof. Goslings welcomed the members of the Heberden Society.

Dr. Van Breemen gave the following dinner toast:

Mr. Chairman, my fair ladies, and gentlemen, I am most happy to see so many English colleagues in the campaign against rheumatism in my own country.

The first group of English doctors as students of the rheumatic diseases came to Amsterdam in 1929, when the Dutch Society against Rheumatic Diseases was founded, but I had then already had for many years very valuable connexions with my English colleagues through my friend Dr. Fortescue Fox, president of the International Society of Medical Hydrology. I can tell you without flattery that this co-operation opened quite a new world for me. I owe my education as a rheumatologist partly to France and England, for in my own country it was practically taboo to say anything about rheumatic diseases in distinguished medical circles. Next to Dr. Fortescue Fox I see the ghosts of many English colleagues.

In 1928, this young man, my neighbour, Dr. Will Copeman, came as secretary to the annual general meeting of the I.S.M.H. at Amsterdam, and a congress was held under my presidency. Among the members of that I.S.M.H. congress were many members of the present Heberden Society, and in that year was founded the Ligue Internationale Contre le Rhumatisme.

But the real contact with your society took place when in an unguarded moment I became honorary member of the famous Royal Society of Medicine, and I was asked to come to London to accept my degree. Without a banquet this could of course not take place! and before the banquet I had a very interesting correspondence with the director, Mr. Edwards, who insisted on calling me "professor"; I had to answer him that I did not hold this title in Holland, but he remained very obstinate. The President at that dinner was a Heberden man and he wittily said: Dr. van Breemen of Amsterdam, you are a Dutchman, and that is in England something very special, for we English people are used to say the following: "God damned the world, but Holland dammed itself".

This was much to the point, and I must confess that my

English colleagues are right: we Dutchmen cannot stop making dams and not only in the material sense but also spiritually; every dike is a pillar and not always a pillar of wisdom.

Now please allow me to give this folder with souvenirs about England to you for your historical museum at Portland Place in London, and I propose that we drink all together from this "loving cup", a present given to me in 1938 on the tenth anniversary of the foundation of the Ligue Internationale Contre le Rhumatisme, and offered by Mrs. Copeman on behalf of the English members. I hope that Professor Formyne will allow us to drink every ten years from this cup!

Replying on behalf of the Heberden Society, the President, Prof. J. H. Kellgren, thanked the speakers for their welcome and hospitality, congratulated them on the excellence of the scientific programme they had arranged, and expressed the hope that this meeting would set a precedent for further equally successful joint meetings in Great Britain and the Netherlands.

### A.D.A.R.

#### ASOCIACIÓN DE AYUNDA AL REUMÁTICO

A new association for the support of research, treatment, and education in the field of rheumatic disease was founded in Buenos Aires on June 18, 1958.

Full information regarding the aims and constitution of the association may be had from the President:

Elena Luro de Arana, Juncal 783, Buenos Aires, Argentina.

### "AIR"

#### ARCHIVES OF INTERAMERICAN RHEUMATOLOGY

This is a new journal published in Brazil and edited by Drs. Bonomo and Mizraji, with the help of a strong editorial board representative of all parts of the Americas. It enjoys the blessing of the Pan-American League, whose President contributes a foreword. All the contents are in three languages—English, Spanish, and Portuguese. A criticism of the standard of translation into English in some places is perhaps justified.

This issue contains eight articles on subjects which range from the electrophoretic study of serum proteins in rheumatic fever, to the treatment of rheumatoid arthritis with Benemid. These are

mostly well written and interesting (although it is unfortunate that parts of two of them have been printed upside down!). There are also valuable abstracts of the contents of the other rheumatism journals of the world, a "Question and Answer" section of lesser value, and an interesting "Miscellaneous" section, which concludes this rather bulky but well-produced volume. The last contains *inter alia* an account of the IX International Congress of Rheumatology held in Toronto in June, 1957, and the report of the Committee on Nomenclature of the International League against Rheumatism.

W.S.C.C.

### NEW YORK RHEUMATISM ASSOCIATION

#### Officers, 1958-59

At the Annual Meeting of the New York Rheumatism Association held on April 8, 1958, at Cornell University, the following officers were elected:

*President:* Dr. Edward W. Lowman

*Vice-President:* Dr. Emanuel Rudd

*Secretary-Treasurer:* Dr. Albert W. Grokoest, 622 West 168th Street, New York 32, N.Y.



## GAIRDNER CHARITABLE FOUNDATION

The Gairdner Charitable Foundation was incorporated in December, 1957, as a charitable corporation under the laws of the Province of Ontario of the Dominion of Canada. Its funds derive from the personal gifts of Mr. J. A. Gairdner, a Canadian industrialist and financier and members of his family.

In addition to encouraging and rewarding individuals who have made major contributions to the conquest of disease and the relief of human suffering, the Foundation hopes that these international awards will assist in focusing public, professional, and scientific attention upon two of the most important medical problems facing our modern civilization, and will contribute to improved communication of ideas among leading professional and scientific workers in these fields.

The Foundation has arranged to secure the confidential advice of many prominent medical scientists throughout the world.

### International Awards in Arthritis and Heart Disease

The Gairdner Charitable Foundation announces the establishment of international awards in two classes:

(1) *Gairdner Foundation Award of Merit*.—A prize of \$25,000 to be awarded not more than once in every four years to the individual or group of individuals who in the opinion of the Foundation has made the most outstanding discovery or contribution in the fields of the arthritic, rheumatic, and cardiovascular diseases.

(2) *Gairdner Foundation Annual Awards*.—A series of prizes of \$5,000 each to be awarded in any one year to not more than five individuals who in the opinion of the Foundation have made outstanding discoveries or contributions in the same field.

The awards are prizes for achievement and are not grants for the support of future research.

*Conditions and Purposes*.—All awards will be made solely in the discretion of the Foundation and will not be open to application on the part of potential candidates.

The purpose of these awards is to confer signal and substantial recognition upon those individuals whose recent work or discoveries constitute tangible achievement in the fields of the arthritic, rheumatic and cardio-

vascular diseases. Winners will be free to make personal use of their prizes in any manner of their choice.

Awards may be made to residents of any country without restriction as to nationality and will be payable in Canadian funds.

The first awards will be made during 1958.

Notwithstanding its immediate objectives in the fields of arthritic, rheumatic and cardiovascular diseases, the Foundation may in its discretion reward those who, through discoveries of major importance on other fields of medicine, may contribute to the conquest of disease and the relief of human suffering.

*Travel*.—Where winners accept an invitation from the Foundation to participate in scientific meetings in the city of Toronto, Ontario, Canada, or where winners accede to a suggestion from the Foundation that they visit professional colleagues at research or academic institutions in other countries and as a result travelling expenses are incurred, the amount of the award may be increased appropriately.

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## SOCIETÀ ITALIANA DI REUMATOLOGIA

### Acqui Prizes, 1958

The Acqui Health and Tourist Board announces that the Third Acqui Prize was not awarded in 1957 because none of the work submitted came up to the required standard.

At the Seventh Rheumatology Day held at Acqui on September 29, 1957, papers were given by Professor F. Coste (Paris), Professor M. Ferond (Brussels), and Professor J. Goslings (Leyden).

Two Prizes (value L. 1,000,000 and L. 500,000) will be awarded in 1958, the first for an original, unpublished work on rheumatic disease, and the second for a monograph which may have been published during the year 1958. The competition closes on December 31, 1958.

Full particulars may be obtained from the Azienda Autonoma di Cura di Acqui Terme, Piemonte, Italy.



## ABSTRACTS

This section of the ANNALS is published in collaboration with the two abstracting Journals, ABSTRACTS OF WORLD MEDICINE, and OPHTHALMIC LITERATURE, published by the British Medical Association.

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Pararheumatic (Collagen) Diseases; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with research into the scope and modus operandi of steroid therapy.

### Acute Rheumatism

#### Natural History of Rheumatic Heart Disease in the Third, Fourth, and Fifth Decades of Life.

I. Prognosis with Special Reference to Survivorship. WILSON, M. G., and WAN NGO LIM (1957). *Circulation*, 16, 700. 4 figs, 17 refs.

The natural history of rheumatic heart disease in the third, fourth, and fifth decades of life, with special reference to survival, was studied at the New York Hospital-Cornell Medical Center in the case records of 757 patients out of a total of 1,042 coming under observation since 1916. There were 430 females and 327 males, and at the time of the last follow-up about three-fifths were 30 years of age or over, one-third were over 35, and one-seventh were aged 40 or more. During the period of observation there were 78 deaths in patients who had reached the age of 20—53 from cardiac causes, eight from bacterial endocarditis (before the introduction of antibiotics), and seventeen from other causes or from accidents. The diagnosis was established before the age of 20 years in nearly all the cases, and less than 3 per cent. had recurrent carditis after that age. In four-fifths cardiac enlargement was moderate (not detectable clinically) and in one-fifth it was marked.

Mitral insufficiency was diagnosed in 392 patients. Carditis without other major rheumatic manifestation was observed in one or more attacks in only one-fifth of this group, and was associated with polyarthritis, chorea, or both in about three-fifths. Subcutaneous nodules were observed in 3 per cent. In all except one, cardiac enlargement was moderate. Of twelve deaths in this group, eleven were due to non-cardiac causes and one to bacterial endocarditis. Over the years the murmur regressed in two-thirds of the cases. The over-all average annual mortality was 2.76 per 1,000 compared with 3.1 per 1,000 for the general population. Of the 392 patients, 116 experienced one to five pregnancies.

Physical signs of mitral stenosis and insufficiency, which were present in 269 cases, developed in the majority within 1 or 2 years of an acute attack of carditis. Polyarthritis occurred in one or more attacks in about

one-third, chorea in just under one-third, and polyarthritis with chorea in about one-fifth. Subcutaneous nodules were observed in 9 per cent. In only one-fifth of these cases was there marked cardiac enlargement. There were 29 deaths—eighteen from cardiac causes, five from bacterial endocarditis, and six from non-cardiac causes; four patients died 1 to 5 years after mitral valvotomy. The over-all average annual mortality was 7.8 per 1,000; 93 per cent. of the patients survived to the age of 30 years and 86 per cent. to 40 years. Of this group, 112 patients experienced one to five pregnancies.

In 96 patients there were combined aortic and mitral valve lesions, and in 72 of them cardiac enlargement was marked. One or more attacks of polyarthritis occurred in about one-third, chorea in about one-sixth, and polyarthritis with chorea in rather less than one-half. Subcutaneous nodules were observed in one-third, and in "about one-tenth" the carditis was associated with only minor rheumatic manifestations. Of the 37 deaths, 35 were attributed to cardiac causes. The over-all average annual mortality was 29 per 1,000; 75 of the 96 patients survived to the age of 30 but only 38 to the age of 40. A total of fourteen patients in this group experienced one to three pregnancies.

Increasing cardiac involvement was rarely observed in the absence of recurrent carditis. Cardiac enlargement appeared to be a more important factor in prognosis than the type of valvular lesion. The over-all average annual mortality among patients with moderate enlargement was 3.5 per 1,000 compared with 31 per 1,000 among those with marked enlargement. Of the group with moderate cardiac enlargement at the age of 20, 93 per cent. survived to the age of 40, compared with only 40 per cent. of those with marked enlargement. There was no evidence that sex influenced the prognosis.

C. Bruce Perry.

II. Prognosis with Special Reference to Morbidity. MAGIDA, M. G., and STREITFELD, F. H. (1957). *Circulation*, 16, 713. 2 figs, 6 refs.

In this second paper on the natural history of rheumatic heart disease in the third, fourth, and fifth decades, the authors report the results of a follow-up examination

during the 3-year period 1953-55 of 385 of the original 757 patients, with special reference to prognosis and morbidity. Of the 385 patients (160 males and 225 females), 157 were in the third decade, 176 in the fourth, and 52 in the fifth. There were 173 patients with mitral insufficiency; all were asymptomatic, and in over 70 per cent. there was regression of a long-standing apical systolic murmur. None needed surgical treatment. Of 161 patients with mitral stenosis and insufficiency 27 had symptoms, and of these, thirteen might be considered suitable for surgical treatment; in many of the asymptomatic patients there was regression of murmurs. In 51 patients with mitral stenosis and insufficiency there were associated aortic valve lesions; 33 were asymptomatic, and of the remainder some could be considered suitable for surgery.

The records of the 78 patients who died during the 40-year period of the complete investigation were also analysed with reference to morbidity. In 45 of the 53 in whom death was attributed to cardiac causes, carditis, auricular fibrillation, pulmonary embolism, and pneumonia were important precipitating factors.

In none of the 385 cases was progressive cardiac enlargement observed with advancing age alone; thus there was no evidence that the valve lesion *per se* was a major factor in the causation of cardiac enlargement. Both morbidity and mortality in the third, fourth, and fifth decades appeared to be more closely related to the cardiac enlargement and the cardiac damage sustained in the first two decades of life than to the type of valvular lesion. Factors responsible for deterioration in the symptomatic status after the age of 20 appeared to be active carditis, auricular fibrillation, bacterial endocarditis, pregnancy, pneumonia, and embolic phenomena.

C. Bruce Perry.

**Acute Chorea in Children and Streptococcal Infection.** (Chorées aiguës de l'enfant et maladie streptococcique.) CHAPTAL, J., JEAN, R., CAMPO, C., and BONNET, H. (1957). *Arch. franç. Pédiat.*, 14, 910. 6 figs, 7 refs.

This discussion of the relationship between chorea and acute rheumatism is based on a review of thirty cases of chorea in children seen since 1948 at the Clinic for Children's Diseases, Montpellier. Of these cases, seven were examples of "pure" chorea (but two patients in this group subsequently developed recurrences in which signs of rheumatic carditis appeared), and the remaining 23 cases occurred in children with other evidence of acute rheumatism. In twelve cases, polyarthritides and carditis preceded the onset of chorea by periods varying from several weeks to 4 months, in two acute rheumatism occurred simultaneously with the chorea, and in nine at the onset of the chorea there appeared to be an established lesion of the mitral valve.

The authors advance arguments to support the view that chorea represents a peculiar manifestation of a post-streptococcal state and that it occurs some weeks or even months later in the evolution of this state than does acute rheumatism. It is suggested that the rare but occasional occurrence of acute rheumatism and chorea simultaneously may be explained by the assumption that the

chorea is the sequel to a first streptococcal infection and the acute rheumatism to a second and later infection. It is argued that this view has important bearings on the treatment and prophylaxis, in that "anti-inflammatory" therapy with salicylates or steroids will be useless in straightforward cases of chorea, but that relapses of haemolytic streptococcal infection must be prevented by the administration of penicillin to all patients with chorea, exactly as to those who have had acute rheumatism.

C. Bruce Perry.

**Prevention of Rheumatic Fever by a Campaign against Streptococcal Infection.** (Prévention du rhumatisme articulaire aigu par la lutte contre l'infection streptococcique.) COSTE, F., and CHEVALLIER, J. (1958). *Rev. Rhum.*, 25, 18.

**Clinical Picture of Rheumatic Fever. Diagnosis, Immediate Prognosis, Course, and Therapeutic Implications.** MASSELL, B. F., FYLER, D. C., and ROY, S. B. (1958). *Amer. J. Cardiol.*, 1, 436. 1 fig., 3 refs.

**Evaluation of Clinical and Laboratory Factors in Diagnosis of Acute Rheumatic Fever.** SASLAW, M. S. (1958). *Amer. J. Cardiol.*, 1, 450. 1 fig., 16 refs.

**Complications of Rheumatic Fever.** TIDWELL, R. A. (1958). *Amer. J. Cardiol.*, 1, 464. 9 refs.

#### Chronic Articular Rheumatism (Rheumatoid Arthritis)

**Two Years' Experience of Prednisone in Rheumatoid Arthritis.** FEARNLEY, G. F., BALMFORTH, G. V., and BLATCHLEY, R. (1957). *Brit. med. J.*, 2, 1263. 1 fig., 6 refs.

At the rheumatism clinic of the Gloucestershire Royal Hospital, Gloucester, the authors have been prescribing prednisone for an increasing number of patients with rheumatoid arthritis. They are careful to point out that the observations reported here are derived not from a controlled clinical trial but from a retrospective study of the treatment prescribed for 167 new patients seen during the last 2 years. It is the practice at this clinic to treat mild cases with aspirin and the usual supportive measures and moderately severe cases with aspirin and topical injections of hydrocortisone; for the severe cases until recently cortisone was prescribed. During the past 2 years eight such cases originally treated with cortisone have been transferred to prednisone, and with increasing experience some milder cases are now treated with prednisone from the beginning. The standard dosage is 5 mg. 8-hrly (15 mg. daily) and the results are assessed in terms of improvement in functional status and of subjective improvement.

Among the 47 cases treated with prednisone there was a considerable movement from lower to higher categories of functional status, sixteen out of thirty women and nine out of seventeen men showing such improvement. Subjective improvement was reported by 43 (90 per cent.) of the patients and this is much higher than "the inevitable

60 per cent." which is to be expected with any form of diligent therapy in rheumatoid arthritis. Side-effects were frequent and of the usual type; the most troublesome was dyspepsia, which occurred in 23 per cent. of cases, while obesity was noted in four cases, hypertension in two, and diabetes in one. The authors consider that prednisone gives relief from symptoms, that this relief is sustained, and that the advantages of the treatment outweigh its not usually severe side-effects.

William Hughes.

**Treatment of Rheumatoid Arthritis Complicated by Chronic Hypercortisonism, and the Theoretical Causal Role of Certain Amine Oxidases.** SCHERBEL, A. L., HARRISON, J. W., and ATDJIAN, M. (1957). *Cleveland Clin. Quart.*, 24, 219. 16 refs.

Since it became generally realized that steroid treatment, if applied to rheumatoid arthritis, must be on a long-term basis, attention has been called to the clinical manifestations of chronic overdosage—"hypercortisonism". The undesirable effects to which this is said to give rise include emotional instability, chronic fatigue, muscular aching, inability to concentrate, depression of psychomotor activity, and insomnia. According to the present authors, when this syndrome is well established the withdrawal of corticosteroids may be extremely difficult, and in certain cases in the past has proved impossible, even when prolonged over a period of months. They now report a method of administering a combination of chemotherapeutic agents to patients with progressive and persistent rheumatoid arthritis whereby they claim that these difficulties can be overcome or, when it is used as a routine, are not allowed to arise. Since patients treated by this method show sustained improvement despite a decrease in corticosteroid dosage, they conclude that the disease process is altered significantly by the other drugs used.

The treatment consists in admission to hospital and administration initially of corticotrophin (ACTH) and nitrogen mustard (mustine) intravenously to produce rapid suppression of the basic inflammatory changes in the joints. Once this has been achieved one of the antimalarial drugs, chloroquine or hydroxychloroquine, and small doses of prednisone are given to maintain the degree of suppression obtained. In addition iproniazid is administered to alleviate the central nervous manifestations which are characteristic of the syndrome, and possibly to potentiate the effect of the maintenance drugs. Intra-articular injections of nitrogen mustard and hydrocortisone are also given every other day when joint swelling persists. [For details of dosage the original paper should be consulted.] The patient is discharged from hospital when the symptoms of hypercortisonism have been suppressed, and continues maintenance treatment, under periodic supervision, with prednisone, iproniazid, and the antimalarial drug, together with weekly injections of depot corticotrophin, the dosage of each being gradually reduced.

This method of treatment was applied to sixteen patients with active rheumatoid arthritis complicated by

chronic hypercortisonism, which had developed as the result of their having developed resistance to prednisone and the dose having therefore been progressively increased up to an average of 20 mg. daily. All sixteen are reported to have improved significantly both objectively and subjectively, and only one had to abandon the treatment some weeks after discharge owing to nausea and anorexia caused by chloroquine. The follow-up period for six of these patients is now over 2 years.

The authors point out that the symptomatology of rheumatoid arthritis is characterized both by a mesenchymal reaction and by reactions in the central nervous system, and in the course of an interesting theoretical discussion they postulate certain biochemical changes as constituting the basal abnormality in the disease. They consider that it is the decreased activity of amine oxidases or the increased peripheral activity of certain amines that produces hypercortisonism in such patients.

W. S. C. Copeman.

**Clinical Course and Corticosteroid Excretion of Patients with Rheumatoid Arthritis during Long-term Treatment with Corticotrophin.** SAVAGE, O., CHAPMAN, L., ROBERTSON, J. D., DAVIS, P., POPERT, A. J., and COPEMAN, W. S. C. (1957). *Brit. med. J.*, 2, 1257. 7 figs, 9 refs.

In this study, reported from the West London Hospital, the authors have correlated the clinical course and biochemical findings in 33 female and sixteen male patients with severe active rheumatoid arthritis who were treated with corticotrophin (ACTH) for a minimum period of 6 months. The patients were admitted to hospital for 4 weeks for preliminary assessment of the arthritis and treatment, during which time they were taught the technique of self-injection (subcutaneous) and how to collect and forward to hospital aliquot specimens of the total daily urine for estimation of 17-hydroxycorticosteroid (17-(OH)CS) excretion. It was difficult to lay down an exact dosage as the different batches of corticotrophin differed in strength, this variation being reflected in varying levels of 17-(OH)CS excretion and therapeutic effects. Clinical progress was assessed from three factors which the authors have found reliable:

- (1) erythrocyte sedimentation rate,
- (2) strength of grip, measured by means of an adapted sphygmomanometer,
- (3) degree of tenderness to pressure of selected joints.

It was found that clinical improvement was invariably associated with increased adrenal activity, as shown by a rise of at least 50 per cent. in the urinary 17-(OH)CS excretion. Of the 49 patients, six have had complete remission of the disease, and in all the others activity of the disease was suppressed. Side-effects were frequent (all but three cases) but rarely severe and in only six cases had the treatment to be discontinued. The complications and side-effects were those usually encountered during steroid therapy and included moon face (which was practically universal), androgenic effects, oedema, increase in weight, chemosis, and pigmentation. There



was one death from gastro-intestinal haemorrhage; one patient developed hypertension and four developed glycosuria, one of whom became permanently diabetic. In general, however, the authors consider that, under supervision, self-treatment with ACTH for long periods is practicable, that it is suitable for those severe cases which are not improved by other forms of treatment, and has certain advantages over oral cortisone and its newer analogues. The estimation of urinary 17-(OH)CS excretion is useful in controlling the dosage in long-term cases.

William Hughes.

**Clinical Studies of the L.E. Phenomenon in Rheumatoid Arthritis.** (Études cliniques du phénomène L.E. dans la polyarthrite chronique évolutive.) GOSLINGS, J. (1958). *Reumatismo*, 10, 1.

**Epidemiology and Serology of Rheumatoid Arthritis.** FELDMAN, H. A., MOU, T. W., and WADSWORTH, H. (1958). *A.M.A. Arch. intern. Med.*, 101, 425. 11 refs.

**Puncture Biopsy of the Liver in Rheumatoid Arthritis.** (Puntura-biopsia epatica nell'artrite reumatoide.) ORABONA, M. L., and FILOTICO, M. (1958). *Reumatismo*, 10, 24. 6 figs, 8 refs.

**Polyneuritis in Rheumatoid Arthritis.** (Les polynévrites de la polyarthrite chronique évolutive.) VIGNON, G., and DURANT, J. (1958). *Rev. lyon. Méd.*, 7, 115. 24 refs.

**Intra-Articular Hydrocortisone Acetate in the Interphalangeal and Metacarpophalangeal Joints of the Fingers.** [In English.] WRIGHT, V. (1958). *Acta rheum. scand.*, 4, 40. 1 fig., 5 refs.

**Effect of Gold Therapy on the Histochemistry of the Articular Cartilage.** [In English.] KULONEN, E., MÄKINEN, P., and TELKKÄ, A. (1958). *Acta rheum. scand.*, 4, 60. 5 refs.

**pH Dependence of the Sensitized Sheep Cell Reaction of Sera from Patients with Rheumatoid Arthritis.** HEIMER, R., FEDERICO, O., and FREYBERG, R. H. (1958). *Arthrit. and Rheum.*, 1, 62. 1 fig., 5 refs.

#### (Osteo-Arthritis)

**Intra-Articular Injections of "Hydrocortancyl" (Prednisolone Acetate) in Osteo-Arthritis and Non-Inflammatory Rheumatism.** (Injections intra-articulaires d'hydrocortancyl dans les arthroses et les rhumatismes non inflammatoires.) DUPRÉ, A.-L. (1957). *Rhumatologie*, 268, No. 6. 7 refs.

**Clinical Symptoms and Pathology in Osteo-Arthritis of the Hip.** (Arthrosis deformans coxae—Klinik och patologisk anatomi.) HIRSCH, C. (1958). *Nord. Med.*, 59, 687. 4 figs, 19 refs.

**Conservative Treatment in Osteo-Arthritis of the Hip.** (Arthrosis deformans coxae—Konservativ behandling.) NILSSON, H. (1958). *Nord. Med.*, 59, 689.

**Surgical Treatment in Osteo-Arthritis of the Hip.** (Arthrosis deformans coxae—Kirurgisk behandling.) WIBERG, G. (1958). *Nord. Med.*, 59, 690. 2 figs.

**Diagnostic Evaluation in Osteo-Arthritis.** EDWARDS, W. R. (1958). *J. med. Soc. N.J.*, 55, 166. 5 refs.

**Treatment of Osteo-Arthritis with Particular Reference to the Use of Prednisolone.** WILLIAMS, G. T. (1958). *J. Louisiana med. Soc.*, 110, 124. 13 refs.

#### (Spondylitis)

**Ankylosing Spondylitis and Chronic Inflammatory Lesions of the Intestines.** STEINBERG, V. L., and STOREY, G. (1957). *Brit. med. J.*, 2, 1157. 20 refs.

In this paper from the London Hospital, the authors present the clinical details of six patients, five men and one woman, aged from 42 to 50, in whom chronic inflammatory lesions of the intestines were associated with clinical and radiological evidence of ankylosing spondylitis (although in two cases only the sacro-iliac joints and the symphysis pubis were involved). In four of the six cases the clinical, radiological, and sigmoidoscopic picture was that of chronic ulcerative colitis and in these four cases this disease had been present for some years before the onset of back pain. The one female patient had histologically proved Crohn's disease and was found, radiologically, to have ankylosing spondylitis involving the sacro-iliac joints and pubic symphysis; she developed chronic ulcerative colitis 2 years later. The 6th patient also had Crohn's disease and in this case the radiological appearances of ankylosing spondylitis developed in both sacro-iliac joints 9 years later.

The authors consider that the association between ulcerative colitis and ankylosing spondylitis is not fortuitous and suggest that ankylosing spondylitis represents a non-specific reaction to disease of the intestines.

J. Warwick Buckler.

**Rest or Movement Therapy in Ankylosing Spondylitis.** [In English.] LENOCH, F., POLAKOVA, Z., and TRUHLÁŘ, P. (1957). *Rev. Czech. Med.*, 3, 226. 52 figs, 9 refs.

**Involvement of the Heart in Ankylosing Spondylitis.** (Beteiligung des Herzens bei der Spondylarthrit. ankylopoetica.) GAMP, A., and OGORREK, I. (1958). *Z. Rheumaforsch.*, 17, 53. 26 refs.



**Peripheral Joint Manifestations with Ankylosing Spondylo-Arthritis.** (Periferní projevy kloubní při ankylosující spondylartritidě.) TRUHLÁŘ, P. (1958). *Čas. Lek. čes.*, 97, 509. 14 refs.

#### (Miscellaneous)

**Syndrome of Osteoporosis in Africans and its Relationship to Scurvy.** GRUSIN, H., and SAMUEL, E. (1957). *Amer. J. clin. Nutr.*, 5, 644. 1 fig., 28 refs.

The authors have investigated the association of osteoporosis and scurvy among the South African Bantu, only patients being selected for study in whom radiography of the spine showed crush fractures or biconcave vertebral bodies in association with osteoporosis for which no obvious cause could be found; those with radiological evidence of only diminished bone density were excluded. During a period of one year sixteen patients (twelve male and four female) at the Baragwanath Hospital, Johannesburg, fulfilled these criteria; all but two of these were under 60 years of age. The results of clinical, radiological, and laboratory studies are presented, together with the post-mortem findings in two patients who died. Liver biopsy revealed gross haemosiderosis in all of seven patients examined and portal fibrosis in six of them; tests of liver function showed that this was grossly abnormal, the albumin:globulin ratio of the serum proteins was reversed, but the serum calcium and plasma phosphorus levels were within normal limits, except in two cases in which the serum calcium level was below normal.

Of the sixteen patients, nine were also suffering from acute scurvy, one had a haemorrhagic pericardial effusion which was considered to be a "scorbutic equivalent", and one had a past history of scurvy; thus eleven patients (69 per cent.) were or had been scorbutic; the remaining five patients presented no evidence of past or present scurvy. The administration of 500 mg. ascorbic acid daily by intramuscular injection resulted in the complete disappearance of the signs of scurvy within 4 to 6 weeks. This treatment, together with 15 g. calcium gluconate daily by mouth, was continued in six patients for a long-term trial; after observation for 9 months to 3 years all except one showed progressive increase of osteoporosis, as judged by further vertebral collapse.

It is generally accepted that a low dietary intake of calcium, abnormal blood protein levels, haemosiderosis, and scurvy are among the factors which, singly or together, may be responsible for osteoporosis. The authors point out, however, that these conditions, with the exception of scurvy, are common to the majority of African patients. In fact both scurvy and osteoporosis are uncommon diseases at this hospital, yet these relatively rare conditions were frequently found in the same patient. Moreover, the incidence of osteoporosis among a group of 48 patients with typical acute scurvy was 18.7 per cent., whereas no case of osteoporosis was found in a group, selected at random, of 150 non-scorbutic subjects of the same age and sex. In the authors' view the evidence suggests that chronic

deficiency of ascorbic acid, often unrecognized, may be responsible for osteoporosis in the Bantu.

Joseph Parness.

**Reiter Syndrome in Females. Three Cases.** REIFEM, O. (1957). *Acta rheum. scand.*, 3, 282. 14 refs.

Few cases of Reiter's syndrome in females have been reported. In this paper three such cases are described. The first patient, aged 41, had acute polyarthritis and bilateral conjunctivitis, lasting 2 months. There was gradual improvement with exercise treatment in bed, but 6 months after discharge from hospital, there was a relapse, which was associated with a vulvo-vaginitis. In the second patient, aged 34, the polyarthritis and conjunctivitis developed about 3 weeks after an attack of acute epidemic diarrhoea. Slight vulvitis was present. The third patient, aged 55, had a yellow vaginal discharge, acute polyarthritis, and photophobia without definite conjunctivitis. In all three cases the erythrocyte sedimentation rate was raised, but the results of other investigations were negative. Urethritis was present in the first case only, and the author suggests that vulvo-vaginitis should be accepted as a cardinal feature of the syndrome.

K. C. Robinson.

**Functional Disturbances of the Stomach, Pancreas, and Liver in Rheumatism.** (К вопросу о функциональных нарушениях желудка, поджелудочной железы и печени при ревматизме.)

NIKOLAIEVA, V. A. (1957). *Ter. Arh.*, 29, 68. 11 refs.

A study of gastro-intestinal disturbances occurring in 100 cases of "rheumatism" [? rheumatoid arthritis] in 23 men and 77 women, mostly under 40, is reported. During the active period of the disease there were various dyspeptic symptoms, the most common being lack of appetite. Hypochlorhydria was frequently present. Functional disturbances of the pancreas were slight and usually disappeared when adequate antirheumatic therapy was given. Investigations of liver function indicated that its antitoxic and prothrombin-forming activities were more frequently affected than those functions concerned with carbohydrate metabolism.

A. Orley.

**"Unexplained" High Erythrocyte Sedimentation Rate.** ANSELL, B., and BYWATERS, E. G. L. (1958). *Brit. med. J.*, 1, 372. 15 refs.

Over a period of 3½ years the erythrocyte sedimentation rate (E.S.R.) was determined by Westergren's method in some 900 new cases of rheumatism at Hammersmith Hospital (Postgraduate Medical School of London). In 51 of these there was an inexplicably high E.S.R. of more than 29 mm. in one hour. Of these 51 patients, 45 were re-examined, the E.S.R. being determined again within one month of the first visit. It was found that in fourteen of the patients the E.S.R. had returned to normal. Of the 31 in whom the E.S.R. remained high, eight developed typical rheumatoid arthritis, six were probably suffering from this disease, and in six other disease processes were diagnosed. In eleven instances

no cause could be found for the raised E.S.R., and the general health of these patients has continued good.

Discussing these findings, the authors emphasize that a raised E.S.R. should call for a careful assessment and investigation of the patient, although it is not necessarily associated with a bad prognosis, particularly in older patients.

A. W. H. Foxell.

**Attempt to Induce Rheumatic Lesions in Animals.** (Proba wywołania zmian gośćcowych u zwierząt.) KRZYMIEN, H. (1957). *Pol. Arch. Med. wewn.*, **27**, 1649. 6 figs, 7 refs.

**Treatment of the Schönlein-Henoch Syndrome.** (Zur Behandlung des Schönlein-Henoch-Syndroms.) TILLING, W. (1958). *Ärzt. Wschr.*, **13**, 121. 44 refs.

**Glomerulonephritis during Schönlein-Henoch Purpura.** (Glomerulonefritidy při schoenleinově-henochově purpře.) VOLEJNÍK, J., and ZAJÍČEK, M. (1958). *Čsl. Pediat.*, **13**, 108. 7 refs.

**ACTH and Cortisone Therapy in Schönlein-Henoch Purpura.** (ACTH- und Cortisontherapie bei der Purpura Schoenlein-Henoch.) MENZI, P. (1958). *Ann. paediat. (Basel)*, **190**, 94. 36 refs.

**Problem of Therapeutic Evaluation in Rheumatoid Arthritis.** WALLACE, S. L., and RAGAN, C. (1958). *Arthrit. and Rheum.*, **1**, 20. 14 refs.

**Pseudorheumatic Syndromes in the Clinical Picture of Cancer of the Lung.** (Sindromi pseudoreumatiche nel quadro clinico del cancro del polmone.) RUGGIERI, E. (1958). *Quad. Chir.*, **1**, 5. 44 refs.

**Psoriatic Polyarthrit.** (La polyarthrite psoriasique.) COSTE, F. (1958). *Z. Rheumaforsch.*, **17**, 90. 79 refs.

**Arthritis and Automobile Accidents.** KULOWSKI, J. (1958). *Rheumatism*, **14**, 28. 4 figs, 47 refs.

#### Gout

**Studies of Hyperuricemia produced by Pyrazinamide.** CULLEN, J. H., LEVINE, M., and FIORE, J. M. (1957). *Amer. J. Med.*, **23**, 587. 7 figs, 15 refs.

Following reports of the development of clinical gout in patients receiving chemotherapy for tuberculosis the authors, working at Albany Medical College, Albany, New York, have further investigated the effect of pyrazinamide and PAS on uric acid levels in the blood and urine. The subjects comprised ambulatory male patients [number not stated] aged from 23 to 68 years from the general medical wards and five tuberculous patients receiving long-term therapy with pyrazinamide and isoniazid; patients receiving uricosuric agents or showing evidence of renal or hepatic disease were excluded from the study. Pyrazinamide 3 g., isoniazid 300 mg., PAS 12 g., and probenecid 2 g., were given daily in various combinations, at first for 7-day periods and subsequently in some cases for 14 days. Samples of blood for serum

uric acid estimations were obtained 16 hours after the last dose of the drugs, and the accuracy of the 24-hour urine volumes (since the patients were ambulatory) was checked by creatinine estimations. The method of Dubbs and others was used for the determination of uric acid levels and that of Alvine and Miller for inulin clearance.

Pyrazinamide caused a fall in the urinary output of uric acid by the second day and a rise in the serum uric acid level, which reached a peak between the 5th and 7th days. This was unaffected when isoniazid was then given in addition, but when both drugs were discontinued the serum uric acid level fell and the urinary output rose. Inulin clearance results showed no alteration in the glomerular filtration rate during or after therapy. When pyrazinamide and isoniazid were given together from the outset a similar result was obtained; there was no change when isoniazid alone was withdrawn, but a fall in the serum uric acid level and a rise in urinary uric acid content occurred when pyrazinamide was withdrawn.

In one of the three subjects receiving pyrazinamide in addition to PAS and isoniazid, a similar result was recorded, but in the other two the rise in the serum uric acid level and the fall in urinary uric acid output was less, and marked changes did not occur until 7 days after withdrawal of the PAS. Four patients received pyrazinamide and isoniazid for a long period and three were given this combination for one week, all being then given PAS; in three (two receiving long-term and one short-term treatment) no effect was noted, while in the other four there was a fall in serum uric acid level and a rise in urinary output. Probenecid, which was given with pyrazinamide in four cases, appeared to suppress the hyperuricaemia in two of them and in the other two to delay it; in all four there was a rapid rise in serum uric acid level when probenecid was stopped while the administration of pyrazinamide was continued. Lastly, of four tuberculous patients receiving long-term therapy with pyrazinamide, three showed no change on receiving probenecid and one showed some response, this being the subject who had previously responded to PAS. In one case ACTH (corticotrophin) was given after treatment with pyrazinamide for 8 days and this caused a marked urinary excretion of uric acid and fall in the serum uric acid level.

The authors conclude that the rise in serum uric acid concentration following administration of pyrazinamide is due to decreased excretion of uric acid in the urine, which in turn is presumably the result of increased tubular reabsorption. The hyperuricaemia was unaffected by isoniazid, reduced in some cases by PAS and by probenecid, and completely reversed in the one patient treated with ACTH.

B. M. Ansell.

**Hyperuricemia due to Pyrazinamide.** SHAPIRO, M., and HYDE, L. (1957). *Amer. J. Med.*, **23**, 596. 1 fig., 11 refs.

At the University of California, Los Angeles, the authors have investigated the reported hyperuricaemic effects of pyrazinamide in 46 patients suffering from pulmonary tuberculosis (but with normal renal and hepatic

function) who were receiving various combinations of the following drugs: streptomycin 1 g. intramuscularly twice weekly, isoniazid 300 mg. daily, PAS 12 g. daily, and pyrazinamide 1.5 or 3 g. daily. Throughout the study the patients were given their usual diet. A group of ten similar patients not receiving pyrazinamide served as controls. Serum uric acid determinations were performed by a modification of Koch's method.

In the 46 patients who were receiving pyrazinamide, the serum uric acid level was persistently between 6.2 and 9.7 mg. per 100 ml. compared with a level of less than 5.5 mg. per 100 ml. in the controls. This occurred whether the daily dose of pyrazinamide was 1.5 or 3 g. Further, of eleven new patients treated with pyrazinamide and isoniazid, all showed a rise in serum uric acid level whichever dosage of pyrazinamide was employed, and a further eight patients receiving streptomycin and isoniazid all showed a rise in serum uric acid level 48 hours after the addition of 3 g. pyrazinamide daily to the regimen. In five treated with isoniazid and PAS, the addition of pyrazinamide caused only slight changes in the serum uric acid level at 48 hours, but a definite increase after 9 days. One patient under treatment with streptomycin and isoniazid and who was also receiving sodium salicylate for arthritis did not develop hyperuricaemia on the addition of pyrazinamide, nor did two patients given salicylates before and during the administration of 3 g. pyrazinamide daily.

The authors conclude that pyrazinamide in a dosage of 1.5 or 3 g. daily causes a persistent hyperuricaemia which is delayed but not prevented by the administration of PAS and is unaffected by other antituberculous drugs. The hyperuricaemia is, however, prevented by salicylates. It is noted that none of the patients studied complained of joint pains, nor were any attacks of gout observed.

B. M. Ansell.

**Vascular Changes in the Acute Attack of Gout and the Favourable Effect of Their Modification.** (Alteraciones vasculares en el ataque agudo de gota e influencia favorable de su modificacion.) JÜNEMANN B., C., DOMINGUEZ A., R., BERRIOS DE LA L., R., MELENDEZ E., O., ACEVEDO, E., and CASTILLO, P. (1957). *Rev. méd. Chile*, **85**, 355. 3 figs, 33 refs.

The authors, writing from the University of Chile, Santiago, review the anatomy and physiology of capillary arteriovenous shunts in the peripheral circulation in man, as described by Chambers and Zweifach, Vogler, and others, and discuss the theory of Wood (*Brit. med. J.*, 1950, **1**, 562) that these small anastomoses are implicated in the production of the pain, heat, and redness of the para-articular skin in acute gout. In the normal leg the amplitude of pulsation recorded by an oscillometer decreases with the distance from the trunk. In the leg affected by acute gout, however, the authors have confirmed the findings of Wolfson and Robinson (*J. Lab. clin. Med.*, 1951, **38**, 951) that pulsation in the inferior tibial region is greater than that in the femoral region.

"Hyderyne" (a preparation of ergot alkaloids) in a dose of 2 ml. was injected into the femoral or brachial artery of the affected limb in four cases of acute gouty

arthritis, smaller doses being subsequently given, first by intramuscular injection and then by mouth, for periods up to 15 days. In a further four cases the initial intra-arterial injection was omitted, but the treatment was otherwise the same. An improvement was observed in the affected joint within 5 minutes of the intra-arterial injection of hyderyne, the skin becoming pale and the part less painful, while the abnormal oscillometer gradient was reversed. The peri-arterial injection of procaine did not produce the same effect. In the second group of cases the action of hyderyne was less spectacular, but the treatment was considered to produce a similar degree of improvement [there were no controls] in about 2 days, after which it was continued for maintenance purposes. In neither group were the symptoms completely abolished by hyderyne therapy.

Allan St. J. Dixon.

**Renal Function in Gout.** GUTMAN, A. B., and YÜ, T'SAI FAN (1957). *Amer. J. Med.*, **23**, 600. 13 figs, 45 refs.

There is still confusion as to the role of the kidney in the pathogenesis of gout. The original concept suggested by Garrod (*Med.-chir. Trans.*, 1848, **31**, 83) of a specific renal lesion was supported by other early studies of urate clearance. However, subsequent workers have found an occasional patient with an abnormally high excretion of urate.

The present authors, working at Mount Sinai Hospital, New York, have therefore undertaken extensive investigations of the renal function in 300 patients suffering from primary gout in various phases of the disease; the ages of the patients ranged from 25 to 79 years and all but nine were male.

As judged by the results of routine urine analysis, the urine concentration test, phenolsulphonthalein excretion, and the serum non-protein nitrogen level, 65 patients, mostly in the older age group, had overt renal damage and many of these also showed evidence of vascular disease elsewhere. In addition, 27 patients had nephrolithiasis and sixteen had hypertension without evidence of impaired renal function. In all cases 24-hour collections of urine were made after the patient had been receiving a low-purine diet, and the value for urate excretion was based on the mean result of analyses of at least two 24-hour collections. Inulin and urate clearances were measured in 150 gouty and twelve non-gouty subjects, para-aminohippurate (PAH) clearance in 110 of the gouty subjects concurrently, and in fourteen cases  $Tm_{PAH}$  was also measured. In addition, the one-hour clearance of urate and creatinine was observed in 64 gouty males, 49 healthy males, and 52 healthy females. The determinations of the urate level in the blood and urine were made by a modification of the colorimetric method of Buchanan and others, incorporating the use of uricase.

There were wide variations in inulin clearance. Comparison of the distribution of the results with those for non-gouty subjects showed a close general correspondence, particularly in the older patients, in whom a reduction in inulin clearance was probably related to degenerative changes in the renal vasculature associated with ageing. The PAH clearance studies revealed a



moderate but significant reduction in effective renal plasma flow in the patients with gout, the exact significance of which is not obvious. The four patients in whom the lowest  $Tm_{PAH}$  values were obtained all had presumptive renal vascular disease. There was a general increase in the filtered urate load, which was more pronounced in those with serum urate levels above 8 mg. per 100 ml. When the filtered urate load was within the low normal range it was associated with advanced age or systemic vascular disease. The rate of urinary urate excretion varied considerably in the 150 gouty subjects studied, being greater than the mean range in thirty cases, in which also the mean plasma urate level was higher than in the remainder; however, the majority of the results fell within the normal range, despite some evidence of renal impairment. Tubular reabsorption of urate in the 150 gouty subjects showed wide variations, its magnitude being a linear function of the filtered urate load; there was no difference in the range from that in the controls. The available clearance data do not suggest a tubular excretion of urate, but rather that the filtered urate load is normally largely reabsorbed and that the fraction excreted in the urine is derived from tubular secretion. Urate clearance was usually within the lower limit of normal variation.

The 24-hour urinary urate excretion showed a very much wider range than in normal subjects, and was excessive in 87 cases. The 54 patients in whom excess urate excretion was particularly marked were free from renal damage, belonged to the relatively young age groups, and tended to have a higher serum uric acid level and a lower incidence of visible tophi. At the other end of the scale a low urate output was usually associated with renal impairment. In a few cases it was possible to demonstrate that an observed progressive decrease in urate excretion was the result of deterioration in renal function.

Thus in most gouty subjects the authors demonstrated normal discrete renal functions, but with advancing age and longer duration of the disease the glomerular filtration rate declined and there was also some deterioration in tubular function, these changes being followed by renal retention of urate. They were unable, however, to demonstrate a primary defect in tubular function causing enhanced tubular reabsorption or deficient tubular secretion of urate, and therefore conclude that there is no primary renal defect in gout. They suggest that the hyperuricaemia is an expression of an inborn error of metabolism profoundly affecting some aspect of intermediary purine metabolism and leading to overproduction of urate.

B. M. Ansell.

**Mode of Action of Colchicine in Attacks of Gout.** (Du mode d'action de la colchicine dans l'attaque de goutte.) MUGLER, A. (1957). *J. belge Méd. phys. Rhum.*, 12, 49. 5 figs, 41 refs.

As a remedy for gout colchicine has been in use since the 5th century, but its mode of action is still little understood. In studies of this drug at the Faculty of Medicine of Strasbourg, the author has been impressed by its anti-allergic properties when given intravenously.

In some ways it behaves like adrenaline; thus a dose of 3 mg. may raise the arterial blood pressure by 10 to 20 mm. Hg in normal individuals, and in those who are hypotensive from shock by as much as 40 mm. Hg. The drug also potentiates the action of adrenaline. The above dose will produce a fall in the number of circulating eosinophil granulocytes to the level obtained by the intravenous infusion of 1 mg. of adrenaline (25 mg. ACTH will result in a much greater fall). When the intravenous infusion of colchicine (3 mg.) is repeated several times at intervals of 24 hours there is a rise in the urinary excretion of dehydroandrosterone and 17-ketosteroids.

An acute attack of gout is characterized by intense dilatation of the small vessels and by interstitial oedema, comparable to the conditions seen in serum arthritis. Pain is particularly severe in areas where the surrounding tissues are dense, while relief is felt the moment there is diminution in the swelling of the interstitial tissue. In therapeutic doses colchicine causes vasoconstriction at skin level—an observation which can be confirmed in urticarial oedema. It also reduces capillary permeability. When given intravenously colchicine causes blanching of the affected tissues within 5 to 10 minutes, thus producing an adrenaline-like effect. The second stage of its action may be delayed for several hours and corresponds to the time required for the drug to permeate the nervous system; its ACTH-like effect appears to belong to this second stage.

D. Preiskel.

**Scapulo-Humeral Periarthritis and Gout.** (Periarthritis escapulo-humeral y gota.) MORENO, A. R., and TISEYRA, O. C. (1957). *Arch. argent. Reum.*, 20, 176. 7 refs.

**Acute Gout in Women.** (A propos de la goutte aigue feminine.) GRABER-DUVERNAY, J., and GRABER-DUVERNAY, B. (1957). *Rhumatologie*, 261, No. 6. 32 refs.

#### Pararheumatic (Collagen) Diseases

**Lupus Erythematosus Cell and Its Significance.** WILKINSON, M., and SACKER, L. S. (1957). *Brit. med. J.*, 2, 661. 2 figs, bibl.

The results obtained over a 3-year period with the L.E.-cell test in patients suffering from lupus erythematosus and in patients with other diseases are reported in this paper from the Postgraduate Medical School of London. Two techniques were used:

- (1) Defibrinated blood was incubated for 2½ hours at 37° C., then centrifuged, smears being obtained from the leucocyte layer;
- (2) normal leucocytes were suspended in the patient's serum, incubated for 2½ hours at 37° C., and centrifuged, smears being then made from the leucocyte button.

In eighteen out of nineteen patients with systemic lupus erythematosus the results of the L.E.-cell test were positive. No relationship was found between the intensity of L.E.-cell production and the severity of the disease,



but it was confirmed that adequate hormone treatment led to a marked reduction in the number of L.E. cells produced. L.E.-cell tests were carried out on blood from 495 patients with diseases other than systemic lupus erythematosus, including nine with cutaneous lupus erythematosus, 106 with rheumatoid arthritis, twenty suffering from drug reactions, 44 from cirrhosis, and a number with many other diseases. A positive result was obtained in one patient only, a young woman with portal cirrhosis.

The authors conclude that the L.E.-cell phenomenon is specific for systemic lupus erythematosus, "but that rare false-positive reactions are seen in cases of hydralazine sensitivity and cirrhosis".

E. G. Rees.

#### Histological Study of Muscle in Dermatomyositis and Related Syndromes. (Étude histologique du muscle dans les dermatomyosites et les syndromes voisins.)

LE COULANT, P., and TEXIER, L. (1957). *Ann. Derm. Syph. (Paris)*, **84**, 377. 10 figs.

In the opinion of the authors the histological changes occurring in muscle in dermatomyositis and the collagen diseases have not been studied in sufficient detail. As a result of studies carried out at the Hôpital Saint-André, Bordeaux, they now report the following findings. In dermatomyositis the initial change is oedema both of the muscle fibres and of the interstitial tissue. In the muscle parenchyma a number of different changes may occur side by side, or may be present in one area and absent in a neighbouring one. These changes consist in loss of transverse striations, granular degeneration of whole fibres or parts of fibres, and the appearance of waxy amorphous masses; vacuoles may be seen in some of the fibres, and the cell nuclei increase in numbers without the occurrence of mitotic figures. The interstitial changes are equally varied; here there may be infiltration of histiocytes and lymphocytes, and plasma cells and eosinophils are sometimes also present; the amount of fibrosis is variable. The vessels show no major alterations.

In early lesions the changes are found only in the parenchyma, but in later lesions they are interstitial as well as parenchymatous, and sheets of lymphorrhage are present. In scleroderma the principal changes are interstitial, with dense infiltrates of lymphocytes and histiocytes followed by fibrosis of the collagen. In acute disseminated lupus erythematosus the oedema is relatively mild, the blood vessels are dilated, their walls are slightly thickened, and the lymphocytic infiltration is perivascular. In polyarteritis nodosa the vessels show thickened, infiltrated walls, sometimes accompanied by endarteritis and thrombosis and fibrinoid degeneration of the collagen. In this condition the changes in the muscle fibres are only slight.

E. Lipman Cohen.

#### Disseminated Lupus Erythematosus. Histopathology, Morphogenesis, and Relation to Allergy. TEILUM, G., and POULSEN, H. E. (1957). *A.M.A. Arch. Path.*, **64**, 414. 10 figs, 28 refs.

This paper gives a general review of the histological findings in fifteen cases of disseminated lupus erythe-

matusus studied at the University Institute of Pathological Anatomy, Copenhagen. It is the authors' thesis that this disease is probably an immunological disorder characterized by material giving a positive periodic-acid-Schiff reaction (and therefore containing carbohydrate which has been produced in reticulo-endothelial cells. They point out that the haematoxyphil bodies typical of the disease give the same reaction, as also do the hyaline thrombi and "wire-loop" lesions of the renal glomeruli and material in the characteristic granulomata and nodular necrotic lesions of the lung, serous membranes, and lymph nodes.

They dissent from Klemperer's hypothesis that an alteration of nucleoprotein is the primary change, and from the idea that the fibrinoid deposits are derived from the circulating blood.

[If it be assumed, as seems most likely, that disseminated lupus erythematosus is an immunological disorder characterized by the presence of a circulating antibody directed against nucleoprotein it follows that this antibody, being a  $\gamma$  globulin, would contain appreciable amounts of carbohydrate which would give a positive periodic-acid-Schiff reaction, and its combination with nucleoprotein and deposition in the tissues along with fibrin would account for many of the features of the disease. In the abstracter's opinion, therefore, the difficulties which the authors find in accepting such an assumption are more apparent than real, and are due to a preoccupation with isolated facets of the disease.]

M. C. Berenbaum.

#### Renal Involvement in Progressive Systemic Sclerosis (Generalized Scleroderma). RODNAN, G. P., SCHREINER, G. E., and BLACK, R. L. (1957). *Amer. J. Med.*, **23**, 445. 8 figs, 44 refs.

The authors report from the University of Pittsburgh School of Medicine the detailed clinico-pathological investigation of nine patients with systemic scleroderma, of whom seven died as a result of malignant hypertension and rapid renal failure; of the other two patients one had only mild renal dysfunction and in the other extensive renal lesions were discovered only post mortem. In the seven fatal cases the termination of the illness was characterized by the development of headaches, failing vision, and hypertension. In some cases uraemic coma and convulsions supervened immediately before death, which occurred within a few months of the clinical recognition of renal involvement. Only three of the patients had not received steroid therapy during the course of their illness. Histological examination of the kidneys in six cases revealed three striking pathological changes, consisting in

- (1) intimal thickening of small interlobular arteries and arterioles.
- (2) fibrinoid necrosis of afferent arterioles and glomerular loops,
- (3) multiple cortical infarcts.

Similar changes were found in the viscera.

Reviewing the literature the authors note that renal involvement in systemic sclerosis is by no means rare,

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although often there may be no clinical manifestations. The precise role of ACTH and cortisone in the development of these renal lesions is discussed, but neither the literature on the subject nor the authors' investigations provide a satisfactory conclusion. There is, however, some evidence that the use of hypotensive drugs may initiate renal failure in patients whose hypertension is related to systemic sclerosis. On the other hand it has been held that the renal changes may result from the hypertension itself—whatever its cause in systemic sclerosis—but the authors describe one case in a patient with typical renal changes who remained normotensive throughout the disease. They conclude that renal involvement in systemic sclerosis occurs more frequently than has been supposed, that this represents true involvement of the kidney in this disease, and that the ensuing malignant hypertension, although it adds its particular signature to the renal pathology, does not account for all the changes that may be demonstrated.

J. N. Harris-Jones.

**Familial Hypergammaglobulinaemia and Systemic Lupus Erythematosus.** LEONHARDT, T. (1957). *Lancet*, 2, 1200. 2 figs, 41 refs.

It is well recognized that there is an association between systemic lupus erythematosus (S.L.E.) and hypergammaglobulinaemia. There is evidence of an inherited tendency in both discoid lupus erythematosus and agammaglobulinaemia. The author of this paper from Malmö General Hospital, Sweden, attempts to demonstrate an inherited tendency for the association of S.L.E. with hypergammaglobulinaemia. He describes four siblings (sisters) out of a family of 14 in which hypergammaglobulinaemia was "strikingly frequent". In two of the siblings a diagnosis of systemic lupus erythematosus was established beyond doubt, and both died from this disease; in one of these, severe relapses occurred following administration of phenylbutazone. S.L.E. was also diagnosed in a third sister (a twin), although the presence of L.E. cells was not demonstrated. The fourth sister, who had received treatment for gonorrhoea, complained of arthralgia; in this patient the erythrocyte sedimentation rate was raised and the results of flocculation tests were abnormal. All four sisters had hypergammaglobulinaemia. Of the fourteen siblings, six were considered to show a moderate increase in the gammaglobulin fraction—0.94 to 1.17 g. per 100 ml.; in four others it ranged from 1.37 to 1.46 g. per 100 ml.; and in one a level of 3.78 g. per 100 ml. was recorded.

In this sibship, therefore, the author found three cases of S.L.E. and a significantly high incidence of hypergammaglobulinaemia in the remainder. It is suggested that the inherited mechanism is a tendency towards overproduction of antibodies and gamma globulin. Once hypergammaglobulinaemia is established unfavourable antigens may provoke S.L.E. In support of this theory the author cites the sibling who, known to have marked hypergammaglobulinaemia, developed classical S.L.E. following treatment with phenylbutazone.

J. N. Harris-Jones.

**Natural History of Polyarteritis.** ROSE, G. A. (1957). *Brit. med. J.*, 2, 1148. 27 refs.

This paper summarizes a report to the Collagen Diseases and Hypersensitivity Panel of the Medical Research Council in which 111 histologically proven cases of polyarteritis nodosa occurring during the period 1946-53 in nine teaching centres in Great Britain are surveyed. The author suggests the presence or absence of pulmonary involvement as a useful basis of classification. In 32 of the cases involvement of the lungs was diagnosed on pathological evidence or from the presence of other features considered to be characteristic of pulmonary polyarteritis, in 66 involvement of the lungs was regarded as absent, in six such involvement was doubtful, and the remaining seven cases presented features differing markedly from those of the remainder. (These last two groups are mentioned only briefly.)

There were 66 patients (41 males and 25 females) in the group without lung involvement. At the time of onset thirty (45 per cent.) had chronic respiratory infection or had recently had an acute upper respiratory infection, and six (9 per cent.) had active or quiescent chronic polyarthritis. Clinical manifestations were varied. Gastro-intestinal pain or haemorrhage occurred in 46 cases (70 per cent.) and muscular pain and tenderness were early and frequent manifestations. Focal indurated nodules, ulcers, or papules of the skin were seen in eighteen cases (27 per cent.) in addition to purpura and other skin lesions. There was evidence of peripheral neuritis in 24 cases (36 per cent.). Arthritis, either acute and transient or of a rheumatoid type, occurred in eighteen cases (27 per cent.). Splenomegaly was present in eight cases. Anaemia, leucocytosis, and a slight to moderate eosinophilia were common. There was evidence of coronary involvement in 32 cases (48 per cent.), but pulmonary manifestations in this group were all attributable to infection or cardiac failure. Renal involvement occurred at some stage in 52 cases (79 per cent.), renal polyarteritis being found at necropsy in 39 out of 54 cases and a specific form of glomerulitis in sixteen. Hypertension did not develop in the acute stage of the latter type of renal involvement, but the three patients who survived this stage developed progressive hypertension and uraemia and died within a year. The renal lesions were the primary cause of death in 65 per cent. of the 55 fatal cases, most of the other deaths being due to coronary or gastro-intestinal polyarteritis. Of the 54 patients not treated with cortisone or corticotrophin, 51 died within 6 months, but in many of these cases the diagnosis was first made at necropsy.

There were sixteen males and sixteen females in the group of patients with lung involvement. Clinically, the main features of pulmonary polyarteritis were those of asthma (with no family history), chronic bronchitis, or pneumonia. In eight cases there was a long previous history of respiratory infection and in six one of rheumatic fever. Haemolytic streptococci were isolated from the sputum in 23 per cent. of the cases in which it was examined. Eosinophilia was observed in a high proportion of cases, frequently reaching 5,000 or more per c.mm. At necropsy gross pulmonary damage was the

rule, either from nodular or caseous lesions or from haemorrhagic pneumonia, infarction, or fibrosis. Microscopical examination showed pulmonary polyarteritis and characteristic necrotizing or granulomatous lesions. The incidence of polyarteritis in other organs and the accompanying clinical manifestations was broadly similar to that in the first group. The mean total survival time was longer in cases with pulmonary involvement than in those without, but the period of survival from the onset of systemic polyarteritis was shorter; this probably accounted for the less frequent finding of hypertension in the former type of case. Of the 32 patients with involvement of the lungs, eight received cortisone or corticotrophin, but only one (treated with cortisone) survived. Pulmonary lesions accounted for 42 per cent. of the deaths and renal lesions for 26 per cent.

The author considers that a preceding chronic or acute respiratory infection, especially with the haemolytic streptococcus, is a factor in the aetiology of polyarteritis nodosa, but that the treatment of such infections cannot be incriminated. The association with rheumatic fever and rheumatoid arthritis is also stressed.

J. Warwick Buckler.

**Cogan's Syndrome associated with Polyarteritis Nodosa.** CRAWFORD, W. J. (1957). *Penn. med. J.*, **60**, 835.

**On Some Neuro-Oto-Ophthalmological Manifestations of Systemic Lupus Erythematosus and Polyarteritis Nodosa.** MACRAE, D., and O'REILLY, S. (1957). *Eye, Ear, Nose, Thr. Monthly*, **36**, 721. 3 figs, 20 refs.

**Sjögren's Syndrome and Disseminated Lupus Erythematosus.** SCHAPOSNIK, F., BERGNA, L. J., and CONTE, A. (1956). *Pren. méd. argent.*, **43**, 897.

**So-Called Cutaneous Type of Periarthritis Nodosa.** RUITER, M. (1958). *Brit. J. Derm.*, **70**, 102. 2 figs, 6 refs.

**Regional Manifestations of Scleroderma.** MESZAROS, W. T. (1958). *Radiology*, **70**, 313. 22 figs, 39 refs.

**Cardiovascular Changes in Visceral Lupus Erythematosus.** (Die cardiovasculären Veränderungen beim viszeralem Lupus erythematosus.) SIEGENTHALER, W. (1958). *Cardiologia (Basel)*, **32**, 161. 9 figs, 58 refs.

**Treatment of Lupus Erythematosus with Antimalarial Drugs.** (Tratamiento del lupus eritematoso con preparados antimaláricos.) HEVIA P., H., and LAMAS G., R. (1957). *Rev. méd. Chile*, **85**, 652. 23 refs.

**Collagen Disease of the Nervous System: with Particular Reference to the Syndrome of Infectious Polyneuritis.** TURRELL, R. C., and ROSEMAN, E. (1958). *Stth. med. J. (Bgham, Ala.)*, **51**, 169. 7 refs.

**Fixation of S<sup>35</sup> in the Skin of Patients with Progressive Systemic Sclerosis.** DENKO, C. W., and STOUGHTON, R. B. (1958). *Arthrit. and Rheum.*, **1**, 77. 1 fig, 7 refs.

#### Non-Articular Rheumatism

**Successful Therapy of Fibrositis.** SMITH, R. T. (1958). *J. Amer. geriat. Soc.*, **6**, 147. 4 figs, 14 refs.

**Clinical and Therapeutic Aspects of Hernia of Fatty Tissue as a Cause of Lumbosacral Fibrositis.** (Consideraciones clínicas y terapéuticas sobre las hernias adiposas pancreáticas como causa de fibrositis lumbosacra.) CARPIO, M. G., URQUIETA T., B., GODOY A., M., and MORALES V., I. (1957). *Rev. méd. Chile*, **85**, 583. 4 figs, 6 refs.

**Radiotherapy of Humero-Scapular Periarthritis.** (Zur Röntgentherapie der Periarthritis humero-scapularis.) WERKGARTNER, F. (1958). *Wien. klin. Wschr.*, **13**, 230. 9 refs.

**Radiotherapy of Humero-Scapular Periarthritis.** (Zur Röntgentherapie der Periarthritis humero-scapularis.) FUCHS, G., and HOFBAUER, J. (1958). *Wien. klin. Wschr.*, **13**, 231.

#### General Pathology

**Rheumatoid Factor in Serum and Synovial Fluid.** KREHL, W. A., BOISVERT, P. L., DE FOREST, G. K., and MUCCI, M. B. (1957). *Yale J. Biol. Med.*, **30**, 30. 13 refs.

A modification of the Rose-Waaler haemagglutination test (Boisvert and others, *Yale J. Biol. Med.*, 1956, **28**, 622) was applied at Yale University School of Medicine to specimens of serum and synovial fluid taken simultaneously from ten patients with rheumatoid arthritis and six with other types of arthritis. In five of the latter cases, the possibility of rheumatoid arthritis had not been finally excluded. The effects of incubating both serum and synovial fluid for one hour at 37° C. with various concentrations of hyaluronidase were studied. This procedure increased the agglutination titre in the case of certain specimens of synovial fluid, the optimum concentration being found to be between 150 and 250 turbidity reducing units per 0.3 ml. fluid in an acetate buffer of pH 6.0, but had no effect on the titre of serum. Similar tests were carried out with  $\beta$  glucuronidase at pH 6.5, but this enzyme had no significant effect.

In three cases of rheumatoid arthritis and one of possible rheumatoid arthritis, tests on serum gave positive



and on untreated synovial fluid negative results; in two cases of rheumatoid arthritis, both serum and synovial fluid gave positive results; and in the remaining ten cases both gave negative results. After hyaluronidase treatment six of the specimens of synovial fluid which had previously given negative results gave a positive result and three others a borderline result. In two of the former and all the latter cases the serum had given a negative response, two of them being cases in which the clinical diagnosis had been doubtful. In a further series of tests synovial fluid from nine subjects without either rheumatoid arthritis or the possibility of such a diagnosis gave negative agglutination responses and only one of these became positive after hyaluronidase treatment.

The authors do not consider that the physical change in viscosity resulting from the incubation of synovial fluid with hyaluronidase is itself responsible for the unmasking effect on the haemagglutination reaction, since preliminary experiments have indicated that treatment with hyaluronidase can convert an atypical haemagglutination pattern into a typically positive one even when a high viscosity is artificially maintained with glycerol or methylcellulose.

E. G. L. Bywaters.

**Effect of Room Temperature on Erythrocyte Sedimentation Rate and its Correction.** MANLEY, R. W. (1957). *J. clin. Path.*, **10**, 354. 3 figs, 3 refs.

It is not generally realized that the erythrocyte sedimentation rate (E.S.R.) may increase twofold with variations in room temperature normally found in wards and laboratories in Great Britain and other temperate climates. The E.S.R. was determined by the method of Westergren on 143 occasions in 33 patients at St. Stephen's Hospital, London. The results obtained over a temperature range of 12-8°C. in fifteen patients are given in a table. It was found that the Westergren E.S.R. was affected "to an important degree" by normal variations in room temperature and to a greater extent and over a greater range than the E.S.R. as measured by Wintrobe's method.

A nomogram for correction of Westergren's method is given.

A. W. H. Foxell.

**Serological Reactions to Polysaccharides in Rheumatoid Arthritis.** GOFTON, J. P., THOMAS, J. W., and ROBINSON, H. S. (1957). *Canad. med. Ass. J.*, **77**, 1098. 12 refs.

The original methods for the demonstration of a "rheumatoid factor" in the serum of patients with rheumatoid arthritis by means of an agglutination reaction were those set out by Rose and Waaler, using sensitized sheep erythrocytes. Singer and Plotz ( ) have since shown that the sheep cells can be replaced by polystyrene globules or latex particles, and Heller that the sensitizing serum can be replaced by Cohn's Fraction II of human serum. [Rheins and others ( ) have shown that  $\gamma$  globulin from the serum of numerous animal species will react with the "rheumatoid factor" and give equivalent results.]

In the present paper from the British Columbia Medical

Research Institute, Vancouver, it is stated that the "rheumatoid factor" will react in a similar way with latex particles treated with chondroitin sulphate, hyaluronic acid, or heparin. Sera from 312 patients, including 71 with rheumatoid arthritis, were examined, the standard latex fixation test being performed simultaneously with latex particles treated with Fraction II, with untreated latex particles, and with latex particles treated with each of the three polysaccharide substances. The results obtained with each method are discussed at some length and it is concluded that the specificity of the tests with the polysaccharides is comparable to that of the standard latex fixation test, though the possibility is admitted "that small quantities of active globulin are present as a contaminant in the various polysaccharide preparations". One important implication of these findings is the possibility that an auto-immune reaction between these polysaccharide components of joint tissues and the "rheumatoid factor" in the serum may supply the basis of the chronic inflammatory process of rheumatoid arthritis.

Harry Coke.

**Fibrinoid of the Subcutaneous Nodules in Rheumatoid Arthritis.** (Über das Fibrinoid im Subcutanknoten bei chronischem Rheumatismus nodosus.) MOVAT, H. Z. (1957). *Virchows Arch. path. Anat.*, **330**, 425. 4 figs, bibl.

From Queens University, Kingston, Ontario, the author reports a morphological and histochemical study of the subcutaneous nodules of rheumatoid arthritis, sections from both paraffin-embedded and freeze-dried material being examined. The usual methods of staining showed some central necrotic material enclosed by layers of fibrinoid, fibrin, and surrounding cells in the familiar pallisade formation. The material described as fibrinoid showed a positive periodic-acid-Schiff (PA-S) reaction but no metachromasia. It gave positive reactions to histochemical tests for tyrosine, tryptophan, cysteine, and cystine. Treatment with hyaluronidase reduced or abolished staining by alcian-blue, but had no effect on the PA-S reaction. Collagenase had no effect, but both trypsin and fibrinolysin interfered with the staining of fibrinoid.

On morphological grounds the author considers that fibrinoid is in fact related to fibrin, since it seemed to exude from blood vessels and to occur near them in recently formed nodules. He also cites as evidence for this view that Mallory's phosphotungstic-acid-haematoxylin stain colours both fibrin and fibrinoid blue. He suggests that the presence of the amino-acids indicates fibrin rather than one of the products of connective tissue, and concludes that these findings afford indirect evidence which suggests that the origin of fibrinoid is from fibrin.

G. Loewi.

**Urinary Excretion of Acid Mucopolysaccharides by Patients with Rheumatoid Arthritis.** DI FERRANTE, N. (1957). *J. clin. Invest.*, **36**, 1516. 1 fig., 22 refs.

An increase in the plasma concentration of acid mucopolysaccharides in cases of rheumatoid arthritis having



been reported by Badin and others (*J. clin. Invest.*, 1955, 34, 1317), the present author, working at the Brookhaven National Laboratory, Upton, New York, has estimated the output of acid mucopolysaccharides in 24-hr specimens of urine from such patients by precipitation with cetyltrimethylammonium bromide and determination of the glucuronic acid content of the precipitate (di Ferrante and Rich, *J. Lab. clin. Med.*, 1956, 48, 491). In a study of eight patients with active untreated rheumatoid arthritis a significant increase above the average normal value was demonstrated. In five of these cases treatment with salicylates (about 4 to 5 g. a day) resulted in a significant fall in mucopolysaccharide excretion.

By treating 20 litres of pooled urine from patients with rheumatoid arthritis a sufficient quantity of mucopolysaccharide was isolated for more detailed analysis by chromatography and electrophoresis and comparison with material derived from healthy subjects. Evidence is adduced in support of the hypothesis that the acid mucopolysaccharides in urine from normal individuals and patients with rheumatoid arthritis are derived from similar substances in the plasma and consist of a mixture of chondroitin sulphate and hyaluronate. *Harry Coke.*

**Isolation of the Rheumatoid Factor. (Preliminary Report.)** [In English.] SVARTZ, N., CARLSON, L. A., SCHLOSSMANN, K., and EHRENBURG, A. (1958). *Acta med. scand.*, 160, 87. 3 figs, 13 refs.

The agglutination of sensitized sheep's erythrocytes or inert particles by the serum from patients with rheumatoid arthritis has been attributed to the presence of a specific "rheumatoid factor", and in this paper from the Karolinska Hospital and Medical Nobel Institute, Stockholm, the authors outline the series of investigations which have led to the isolation of a refined complex which can be said to constitute this factor. The factor was first separated from other similar complexes causing agglutination by the cold precipitation technique and subjected to electrophoretic analysis, which showed it to be a fast-moving  $\gamma$  globulin of a nearly homogeneous nature. By ultracentrifugation with a separation cell the cold precipitate was then divided into a top fraction, containing chiefly globulins with a sedimentation constant of 6 to 7 S, which had no haemagglutinating activity, and an active bottom fraction containing a large amount of globulins with a sedimentation constant of 19 to 22 S. The haemagglutinating rheumatoid factor was thus shown to be bound to a fraction containing macroglobulins. Repeated serial ultracentrifugation failed to further the purification of the factor, which was finally achieved chromatographically by the use of the cation exchanger carboxymethylcellulose. The cold precipitate was dissolved in saline and applied to a column of carboxymethylcellulose, the adsorbed proteins being eluted with a continuously increasing pH gradient. One fraction was isolated that gave a stronger haemagglutination reaction than the rest and on analytical ultracentrifugation showed only a single peak, having a sedimentation constant of 18.7 S. The concentration of this component was found to be almost proportional to the haemagglutinating power of the active fractions. The authors

are therefore able to state that the "rheumatoid factor" is a macroglobulin with a sedimentation constant of 18.7 S which behaves electrophoretically as a fast-moving  $\gamma$  globulin.

[Further analysis of this complex will be awaited with much interest.] *Harry Coke.*

**Electron Microscope Study of the Glomerulus in Nephrosis, Glomerulonephritis, and Lupus Erythematosus.** FARQUHAR, M. G., VERNIER, R. L., and GOOD, R. A. (1957). *J. exp. Med.*, 106, 649. 11 figs, 34 refs.

The structure of the renal glomeruli was examined by the light and electron microscopes in biopsy material from 76 children suffering from nephrosis, glomerulonephritis, and lupus erythematosus. It is pointed out that the normal glomerulus has three components—the endothelium, basement membrane, and epithelium. In the patients with nephrosis there was a loss of the characteristic organization of the epithelial cytoplasm into foot processes. (This was especially marked, and appeared to be the only change, in cases of "pure" nephrosis.) The capillary loop surfaces were covered by broad masses of epithelial cytoplasm. There was also an increase in the number of vacuoles. Swollen endothelium with numerous intracytoplasmic vesicles and some changes in the basement membrane were observed. The glomeruli in glomerulonephritis showed mainly proliferative changes of the endothelium and basement membrane. In the acute stage of the disease the number of endothelial cells was increased; in addition cytoplasmic swelling of both endothelium and epithelium and thickening of the basement membrane with accumulations of "basement-membrane like" material were seen. In the subacute and chronic stages the glomeruli consisted of tangled masses of cells with few open blood channels. The most characteristic finding in lupus erythematosus was a thickening of the basement membrane with some endothelial proliferation. This could be seen before any sign of the "wire-loop" by light microscopy; similarly the changes in nephrosis were seen by the electron microscope before they were detected by the conventional microscope.

In the later stages of these three disease conditions no distinction between them was possible by the electron microscope, the appearances in all three being very similar. As expected, there was a considerable overlap in the appearances in many of the cases. *G. Loewi.*

**Objective Evaluation of Patients with Rheumatic Diseases.**

**III. Comparison of Serum Glycoprotein, Seromucoid, and C-reactive Protein Determinations as Methods for the Evaluation of Patients with Rheumatic Fever.** SHETLAR, M. R., PAYNE, R. W., STRENGE, H. B., and FAULKNER, J. B. (1957). *J. Pediat.*, 51, 510. 3 figs, 12 refs.

A comparative study of the value of various laboratory procedures in the estimation of the severity and duration of disease activity in rheumatic fever was undertaken at the Veterans Administration Hospital and Oklahoma School of Medicine, Oklahoma City. The authors

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determined the serum concentrations of glycoprotein, seromucoid (using tryptophan estimation), and C-reactive protein, and the serum antistreptolysin-O titre, comparing the values obtained with the erythrocyte sedimentation rate (E.S.R.) [method not stated] and the clinical findings. There was some overlapping between patients with "active" and those with "inactive" disease with all these tests, but each one (with the exception of the antistreptolysin-O titre) appeared to be measuring a similar type of change although the changes took place at different rates.

The most rapid response to changes in disease activity was obtained with the C-reactive protein test, the results of which became negative very quickly after clinical disease activity had subsided. The E.S.R. returned to normal more slowly than did the other values; it was raised in thirteen out of eighteen cases of inactive and in fourteen out of sixteen cases of active disease. The serum glycoprotein level, estimated as milligrams of bound hexose per 100 ml. serum or as a percentage of the total serum proteins, was raised in all eighteen cases of active disease, as was the seromucoid level. The former was raised in nine out of the 21 inactive cases and the latter in four out of sixteen such cases. The antistreptolysin-O titre showed no clear relationship with inflammatory activity.

E. G. L. Bywaters.

**Cause of Anomalous Results in the Erythrocyte Sedimentation Rate using Wintrobe's Method.** SHANNON, F. T., and BYWATERS, E. G. L. (1957). *Brit. med. J.*, **2**, 1405. 9 figs, 15 refs.

For the past 5 years the erythrocyte sedimentation rate (E.S.R.) of all in-patients at the Special Unit for Juvenile Rheumatism, Canadian Red Cross Memorial Hospital, Taplow, has been measured every week by both the Westergren and the Wintrobe methods, the total number of duplicate readings thus obtained being approximately 19,000. In order to study the incidence and causes of the anomalously low results sometimes obtained by the Wintrobe method in the presence of a very active disease process the authors have analysed the 2,540 pairs of readings from 100 patients selected at random. This group was mainly composed of children and young adults, of whom forty had rheumatoid arthritis, 47 rheumatic fever or chorea, and the remainder other forms of collagen disease. The results were regarded as discordant if the Wintrobe E.S.R. was less than 20 mm. at a time when the Westergren rate was 50 mm. or more in one hour. In such cases the Westergren rate gave without exception the more accurate reflection of the clinical state. Anomalous readings were obtained by the Wintrobe method on at least one occasion in 26 out of the 100 cases and constituted 4.6 per cent. of the 2,540 readings. On 23 per cent. of the 498 occasions on which the Westergren reading was over 50 mm. in one hour the results were discordant, and in this group of cases the mean packed cell volume (P.C.V.) was 40.6 per cent.; in the remaining 77 per cent. of cases the P.C.V. was 36.5 per cent., the difference being highly significant.

Experiments were then carried out to determine how far the plasma viscosity, the P.C.V., and the internal

diameter of the sedimentation tube were concerned in the causation of anomalous results by the Wintrobe method. Plasma viscosity was measured in a modified Ostwald capillary viscosimeter and expressed in terms of its relation to the viscosity of distilled water as indicated by its rate of flow at 37° C. It was found that as the relative plasma viscosity increased beyond 1.8 the mean Westergren reading rose steadily, whereas the Wintrobe reading increased more slowly to a maximum at a viscosity of 2.1 and thereafter fell again to the level attained at a viscosity of 1.9 to 2. The effect of increasing plasma viscosity on the Wintrobe reading was essentially the same whatever the P.C.V. of the blood. In the lower ranges of viscosity values the Wintrobe readings for blood with a P.C.V. below 39 per cent. were closer to the Westergren readings than those for blood with a higher P.C.V., but there was always a fall in the Wintrobe rate when the plasma viscosity rose above 2.1 or 2.2. The Westergren readings at different levels of viscosity also tended to be somewhat higher with blood of low P.C.V., but remained directly related to the plasma viscosity at all P.C.V. levels. When the P.C.V. was below 40 per cent. the results obtained at different levels of plasma viscosity with a modified Wintrobe tube of 4.5 mm. internal diameter were much the same as those obtained with the standard tube of 2.5 mm. internal diameter. When the P.C.V. was above that level, however, the larger tube gave results more closely resembling the Westergren readings, though the E.S.R. still tended to fall off at the higher levels of plasma viscosity.

The authors conclude that the discrepancy between the results obtained by the two methods is due to the additive effect on the Wintrobe E.S.R. of a high plasma viscosity and the inadequate bore of the standard Wintrobe tube, the discrepancy being more marked when the P.C.V. is over 40 per cent.

R. F. Jennison.

**Mechanism of the Fractional Erythrocyte Sedimentation Rate (F.E.S.R.).** (К механизму фракционной реакции оседания эритроцитов (ФРОЭ)) GAVALOV, S. M. (1957). *Sovetsk. Med.*, **21**, 62. 2 figs, 10 refs.

In 1926 Epshtein introduced the method of fractional determination of the erythrocyte sedimentation rate (E.S.R.), in which the rate of sedimentation is recorded every 15 minutes over a period of 90 minutes and the results plotted as a curve. The type of curve obtained enables the observer to distinguish five types of E.S.R.: the normal, the areactive, the hyporeactive, the reactive, and the hyperreactive.

The hyperreactive curve, distinguished by rapid sedimentation during the first 30 minutes followed by slowing of the rate, is characteristic of acute infections in a highly reactive subject, for example, in acute rheumatism or pneumonia. The reactive type, in which the most rapid sedimentation occurs in the second or third quarter of the first hour, is found in acute infections in subjects with usually normal reactivity. The hyporeactive curve, in which the highest rate is at the end of the first hour, occurs in convalescent patients or in acute infections in subjects with lowered reactivity. The areactive curve is

found in cases of overwhelming infection, or in patients with little or no resistance; in this type the curve is very low and nearly horizontal throughout. In the normal curve, as seen in healthy persons, the rate does not rise above normal levels and successive estimations do not differ by more than 1 to 3 mm. per minute. The author states that it is possible by means of fractional estimation of the E.S.R. to evaluate the stage of the infection and the reactivity of the patient, and the procedure is therefore valuable in prognosis, especially in children.

L. Firman-Edwards.

**Personal Experience of the Value of Serological Tests in the Differential Diagnosis of Rheumatoid Arthritis and Ankylosing Spondylitis.** (La nostre esperienza sul valore delle prove sierologiche per la diagnostica differenziale dell'artrite reumatoide e della spondilite anchilopoietica.) BARCELÓ, P. (1958). *Reumatismo*, 10, 7.

**Hyaluronate in Normal Human Synovial Fluid.** HAMERMAN, D., and SCHUSTER, H. (1958). *J. clin. Invest.*, 37, 57. 1 fig., 16 refs.

**Serum Mucoproteins in Rheumatic Diseases. II.** (Las mucoproteinas sericas en las afecciones reumáticas.) MORENO, A. R., and PAZ, M. A. (1957). *Arch. argent. Reum.*, 20, 118. 3 refs.

**Water and Electrolyte Metabolism in Rheumatic Fever and Rheumatoid Arthritis.** (O niektórych zagadnieniach gospodarki wodnej i mineralnej w chorobie reumatycznej i gośćcu pierwotnie przewlekłym.) RASZEJA-WANIC, B., JASIŃSKI, K., KUBACKI, A., and SMARSZ, C. (1957). *Pol. Arch. Med. wewn.*, 27, 150. 2 figs, 19 refs.

**Renal Function in Rheumatic Fever and Rheumatoid Arthritis.** (O czynności nerek w chorobie reumatycznej i w gośćcu pierwotnie przewlekłym.) JASIŃSKI, K., RASZEJA-WANIC, B., KUBACKI, A., and SMARSZ, C. (1957). *Pol. Arch. Med. wewn.*, 27, 1483. 3 figs, 28 refs.

**Antistreptolysin and Waaler-Rose Reactions as the Basis of a Systematic Classification of the Rheumatic Diseases.** (Streptokokken-Status, Antistreptolysin- und Waaler-Rose-Reaktion als Grundlagen einer systematischen Ordnung rheumatischer Krankheiten.) TICHY, H. (1958). *Z. Rheumaforsch.*, 17, 51. 1 fig.

**Antistreptolysin-O Titre in the Diagnosis of Rheumatic Activity.** [In English.] MING-HSIN, H., and CHENG-WEI, L. (1958). *Chin. med. J.*, 76, 253. 5 figs, 12 refs.

**Clinical Significance of Serum Antistreptolysin-O Levels.** [In English.] HSIOH-TEH, C., and HUA-CH'ENG, W. (1958). *Chin. med. J.*, 76, 259. 2 figs, 7 refs.

**Interaction of Nuclei and Globulin from Lupus Erythematosus Serum demonstrated with Fluorescent Antibody.** FRIOU, G. J., FINCH, S. C., and DETRE, K. D. (1958). *J. Immunol.*, 80, 324. 8 figs, 11 refs.

**Purification of Haemagglutinating Factors in Rheumatoid Arthritic Sera by Cohn's Method 10 and Ultracentrifugation.** [In English.] SWAHN, B., and GRUBB, R. (1958). *Acta path. microbiol. scand.*, 42, 173. 22 refs.

**Abnormalities of Collagen in Neoplastic Diseases of the Lung (with Rheumatic Pains).** (Sulle collagenopatie in corso di affezioni neoplastiche del polmone (con sindrome reumatologica).) AGRESTI, A. (1958). *Quad. Chir.*, 1, 29. 23 figs, 42 refs.

**Thrombosis and Fibrinoid Exudates in the Histogenesis of So-Called Collagen Diseases.** (Thromboses et exsudations fibrinoides dans l'histogénèse des prétendues maladies du collagène.) DE BRUX, J. (1958). *Presse méd.*, 66, 289. 8 figs.

**Role of the Globulin Constituent of Fibrinoid in the Histogenesis and Classification of the So-Called Collagen Diseases.** (Rôle des constituants globuliniques du fibrinoïde dans l'histogénèse et la classification des prétendues maladies du collagène.) DE BRUX, J. (1958). *Presse méd.*, 66, 661. 78 refs.

**Synovial Fluid in Arthritis.** BLUMBERG, B. S. (1958). *Rheumatism*, 14, 37. 5 figs, 52 refs.

#### ACTH, Cortisone, and Other Steroids

**Enhancement of Mantoux Reaction Coincident with Treatment with Cortisone and Prednisolone.** TRUELOVE, L. H. (1957). *Brit. med. J.*, 2, 1135. 20 refs.

Following the observation that a patient with Addison's disease had initially a negative Mantoux reaction at a dilution of 1 in 100 but that this reaction had become positive at a dilution of 1 in 1,000 37 days later while she was receiving a daily maintenance dose of 50 mg. cortisone, the author carried out Mantoux tests on all (24) patients admitted with a variety of disorders to Stoke Mandeville Hospital, Aylesbury, Bucks, who were likely to need corticosteroid therapy and who were Mantoux-negative on admission (at a dilution of 1 in 100 in thirteen cases and of 1 in 1,000 in eleven cases). They comprised fourteen men and ten women ranging in age from 24 to 80 years, the majority being over 60 years old.

In addition to receiving the treatment appropriate to their particular ailment these patients were given either cortisone in doses ranging from 25 to 75 mg. daily or prednisolone 15 to 60 mg. daily. Of the 24 patients, twenty subsequently showed a positive Mantoux reaction, three of them who had previously been negative at a dilution of 1 in 100 becoming positive at 1 in 1,000. In the majority of the cases, the time interval between the two tests was less than 2 weeks. The clinical course of



their disease seemed to have no bearing on the reversion to a Mantoux-positive reaction; thus six of those who reverted showed marked improvement, six showed no change, three deteriorated and subsequently died, and three were not very ill at any time.

A further case, that of a man aged 35 with pneumonia and pleural effusion, is recorded in some detail, in which the Mantoux reaction became positive following recovery of adreno-cortical function which had been depressed during the acute stage of the illness, no steroid drugs having been administered. The suggestion is made that although steroid treatment is able to suppress a positive tuberculin reaction when given in high dosage, it may, when given in lower dosage, actually restore a reaction which has been suppressed by age, infection, or adrenal deficiency.

H. F. Reichenfeld.

**Possibility of Utilizing Androgens and Oestrogens in the Biosynthesis of Adrenal Corticosterones.** (О возможности использования андрогенов и эстрогенов в биосинтезе гормонов коры надпочечников) JUDAEV, N. A., and DRUŽININA, K. V. (1958). *Probl. Endokr. Gormonoter.*, 4, 21. 17 refs.

In addition to the corticosterones the adrenal cortex synthesizes androgens and, to a certain extent, oestrogens, which in some pathological conditions may be stored in considerable quantities. The corticosterones contain 21 atoms of carbon, the androgens 19, and the oestrogens 18. Convincing evidence has been provided by Hechter and Pinkus of the possibility that cholesterol is convertible into corticosteroids, while the present authors have already shown that dehydroisoandrosterone can serve as substrate in the synthesis of corticosteroids. It is therefore reasonable to expect that other steroids with 19 carbon atoms could be converted into corticosterones with 21.

In experiments designed to explore this possibility guinea-pigs (ten in each experiment) were killed and their adrenal glands removed and placed on ice—one from each animal being used for the test and the other serving as control. Slices of the test glands were then incubated in a medium containing androgens or oestrogens, while control slices were incubated in the same medium without such additions. (The medium consisted of Krebs-Ringer-bicarbonate solution, at a pH of 7.3, excluding calcium chloride, but with the addition of sodium fumarate (0.06 per cent.) and magnesium chloride (0.006 per cent.).) After incubation for 3 hours in an atmosphere of 95 per cent. oxygen and 5 per cent. carbon dioxide at 37°C., the steroids were extracted and estimated by Bush's method. It was found that slices of adrenal gland incubated with androstenedione contained double the amount of hydrocortisone found in the control slices. Testosterone was ineffective as a substrate, but the addition of androsterone to the medium produced an even greater synthesis of hydrocortisone, the test slices containing up to treble the amount present in the controls. Oestrone was as effective as androstenedione and oestradiol rather less so. Incubation with adrenosterone caused no increased production of hydrocortisone, but doubled that of cortisone. From

the lower efficacy of oestradiol and testosterone as substrates it is concluded that the presence of the 17-ketosteroid group is of great importance for the transformation of oestrogenic or androgenic steroids into corticosteroids.

L. Firman-Edwards.

**Effect of Cortisone and Corticotropin on the Healing of Gastric Ulcer: an Experimental Study.** JANOWITZ, H. D., WEINSTEIN, V. A., SHAER, R. G., CEREGHINI, J. F., and HOLLANDER, F. (1958). *Gastroenterology*, 34, 11. 2 figs, 11 refs.

From the Mount Sinai Hospital, New York, the authors describe studies designed to demonstrate the effects of ACTH (corticotrophin) and cortisone on the rate of re-epithelization and of the healing of experimentally induced gastric ulcers in dogs.

In the first series of experiments, which were performed on dogs with a Heidenhain pouch, the columnar surface epithelium of the stomach down to the necks of the gastric glands was removed chemically by applying eugenol; mucosal biopsy specimens were taken 2, 4, 6, 8, and 24 hours later, the dogs meanwhile receiving a normal diet and fluid intake. The experimental group had received either ACTH (5 to 10 mg. per kg. body weight) or cortisone acetate (5, 10, or 15 mg./kg.) daily for 3 to 6 days before and on the day of the experiment. Examination of the serial biopsy specimens showed that the administration of ACTH or cortisone did not influence the rate of epithelial replacement, which in both groups of animals was virtually complete in 24 hours.

In the second series of experiments, which were designed to study the deeper processes of healing, portions of the entire thickness of the corpus of the canine stomach, with blood supply intact, were transplanted to the anterior abdominal wall. In this situation, and protected by a metal guard, the gastric mucosa could be inspected frequently in the otherwise intact animal. Circular excision ulcers deep enough to include the muscularis mucosae were then made in the transplants, the diameter of the ulcer being defined by a punch biopsy machine. The healing time of the ulcers was determined to the nearest day, disappearance of the ulcer and reconstitution of the surface epithelial layer being the criteria of healing. The test dogs were similarly treated, but received 5 or 10 mg. ACTH or 2.5, 10, or 20 mg. cortisone acetate suspension daily intramuscularly for 3 days before the production of the ulcer and throughout the period of healing. The mean healing time of these excision ulcers was prolonged by both cortisone and ACTH in the doses employed in this study. In the case of cortisone the delay in wound healing was not directly related to the dosage of the drug. All the ulcers healed eventually, despite the relatively large doses of corticosteroids.

The authors suggest that adrenocortical hormones may increase the process of existing peptic ulceration, apart from any effect they may have in augmenting the gastric secretion of acid and proteolytic enzymes.

T. J. Thomson.



**Preliminary Experience with Triamcinolone ("Leder-cort").** (Primeras experiencias con triamcinolona.) MORENO, A. R. (1957). *Arch. argent. Reum.*, **20**, 164. 2 refs.

#### Other General Subjects

**Rehabilitation Centre and Rheumatic Disease.** ROBINSON, H. S., and BRADLEY, E. J. (1957). *Canad. med. Ass. J.*, **77**, 131. 1 fig.

This paper describes the experience of the authors in treating 117 patients suffering from rheumatoid arthritis and ankylosing spondylitis who were admitted to the Canadian Arthritis and Rheumatism Society's medical rehabilitation centre at Vancouver. In the centre nursing care was not available, and treatment consisted of medical care and re-training by means of physiotherapy and occupational therapy, and guidance by the almoners.

Of 22 patients suffering from ankylosing spondylitis fourteen came in unable to work, and when the report was written, thirteen were at full-time work, one at intermittent work, and only eight were still unable to work.

Of 39 men suffering from rheumatoid arthritis, 34 were

initially unable to work, and only one was working full time. These figures were reversed to the extent that thirteen were got on to full-time work and 21 were still not working.

Of 56 women suffering from rheumatoid arthritis, ten were initially working full time and of the remainder 23 were working part-time and 23 not at all. These figures changed to the extent that 31 returned to full-time work and only twelve remained unable to work.

The authors point out that many of those not yet at work are still salvageable, and that in some cases factors other than the disease prevent their working.

Discussing their results, the authors point out that they are dealing with diseases of an unpredictable course. Many of the patients were dependent, poor personalities, without the will to help themselves. But some of these finally co-operated well after training had started. In spite of such difficulties the work was found to be satisfying and encouraging.

W. Tegner.

**Chloroquine in the Management of Hypersensitivity States.** FULD, H. (1958). *Rheumatism*, **14**, 12. 4 figs, 22 refs.

VARIATIONS IN THE COURSE OF RHEUMATOID ARTHRITIS

BY

P. E. BROWN AND J. J. R. DUTHIE

From the Department of Social and Industrial Medicine, The University, Sheffield, and the Rheumatic Unit, Northern General Hospital, Edinburgh

In previous papers (Duthie, Thompson, Weir, and Fletcher, 1955; Duthie, Brown, Knox, and Thompson, 1957), the course of a group of patients with rheumatoid arthritis after admission to hospital was described. Certain features of the disease with a bearing on prognosis were discussed. Changes in functional capacity and disease activity were considered for the group as a whole and no attempt was made to trace the course taken by individual cases. The figures reproduced in Tables I and II represent the overall status of the group and do not distinguish between cases more or less permanently in a particular grade and cases with a fluctuating course who happened to be in that grade at the time of assessment. The results could equally well be derived from a group in which every member was pursuing an erratic course as from a group in which the majority were steadily improving or deteriorating.

The present communication is concerned with the types of course pursued by individual patients and particularly with the question of whether an appreciable number of cases showed a tendency towards

permanent recovery or towards permanent disablement.

A complete account of the group and the methods of assessment will be found in earlier reports (Duthie and others, 1955, 1957). Functional capacity and disease activity were determined on admission to hospital, on discharge, and at three subsequent assessments approximately 2 years apart. Four functional grades were used:

- Grade I. Fitness for all normal activities;
- Grade II. Moderate restriction of function;
- Grade III. Marked restriction.
- Grade IV. Confined to bed or chair.

Disease activity was assessed as very active, moderately active, or inactive, according to the E.S.R., the haemoglobin level, the presence of signs of inflammation in the joints, and the degree of systemic disturbance.

Changes in functional capacity and disease activity for the group as a whole are shown in Tables I and II.

There was a slight falling off in functional capacity between the first and second and second and third

TABLE I  
FUNCTIONAL CAPACITY ON ADMISSION, ON DISCHARGE, AND AT SUCCESSIVE FOLLOW-UP ASSESSMENTS

Time of Estimation	No. of Cases	Functional Grades (per cent. of total)					
		I	II	III	IV	I + II	III + IV
Admission .. .. .	282	—	35.4	42.6	22.0	35.4	64.6
Discharge .. .. .	282	11.3	64.2	24.1	0.4	75.5	24.5
First Assessment .. .. .	282	28.4	44.0	25.1	2.5	72.3	27.6
Second Assessment .. .. .	258	27.9	42.2	23.6	6.2	70.1	29.9
Third Assessment .. .. .	247	23.5	40.5	26.7	9.3	64.0	36.0

TABLE II  
DISEASE ACTIVITY ON ADMISSION, ON DISCHARGE, AND AT SUCCESSIVE FOLLOW-UP ASSESSMENTS

Time of Estimation	No. of Cases	Disease Activity (per cent. of total)		
		Very Active	Moderately Active	Inactive
Admission .. .. .	282	26.2	63.5	10.3
Discharge .. .. .	282	5.0	59.2	35.8
First Assessment .. .. .	282	3.5	65.6	30.9
Second Assessment .. .. .	258	12.0	61.2	26.8
Third Assessment .. .. .	247	1.2	69.6	29.2

TABLE III

CHANGE OF FUNCTIONAL GRADES BETWEEN SUCCESSIVE ASSESSMENTS (PER CENT. OF TOTAL)

Changes in Grade	Admission to Discharge	Discharge to First Assessment	First to Second Assessment	Second to Third Assessment
Remaining in Same Grade .. ..	39.8	51.4	70.4	78.6
Upgraded .. ..	60.2	32.0	9.3	3.2
Downgraded .. ..	—	16.6	20.2	18.2

assessments. The number of cases graded as inactive increased between admission to hospital and discharge and decreased slightly at the later assessments.

### Fluctuations in Functional Capacity

The cases in a particular grade at the time of assessment were made up of those in that grade at the previous assessment and those arriving from other grades in the interval between assessments. The proportion of cases remaining in the same grade from one assessment to another gives an indication of the stability of the group. 56 per cent. of the cases remained in the same functional grade at the three assessments following discharge, and 79 per cent. remained either in Grades I or II or in Grades III or IV. This indicates a considerable degree of stability, since in fluctuations due solely to chance only 6 per cent. would be expected to remain in the same grade. Details of these movements are given in Table III.

There was an increasing degree of stability between the later assessments which is accounted for by a decline in the number of patients moving into higher grades, whereas the number deteriorating stayed much the same.

It might be expected that stability would vary in some way with the severity of the disability, but the percentage of patients discharged in Grade I, who were in the same grade at the three later assessments, was 56.6, compared with 56.2 per cent. of those discharged in Grade II and 54.5 per cent. of those discharged in Grades III and IV, although the grade at the three assessments was not necessarily the one in which the patient was discharged.

A complete account of all changes in grade between discharge from hospital and the third assessment (mean interval 67.4 months) is given in Table IV (opposite).

247 patients followed 51 different courses out of 256 possible ways in which a case might move through four grades over four assessments. The ten most common courses, illustrated in Table V, account for 67 per cent. of all patients.

Table V shows that the most common course followed by patients discharged in Grade II was to remain in this grade until the third assessment (45 patients). The next most common was to improve after discharge so that the patient was placed in Grade I and remained in this grade at subsequent assessments (35 patients). A small number improved temporarily but were returned to Grade II at the second assessment (13 patients). The remainder were relegated to Grade III at the first (10 patients), second (11 patients), or third assessment (12 patients). Only six of 24 patients discharged in Grade III were subsequently upgraded. Of seventeen patients discharged in Grade I, nine remained in that grade and eight were subsequently relegated to Grade II.

TABLE V

THE TEN COURSES MOST COMMONLY TAKEN BETWEEN DISCHARGE AND THE THIRD ASSESSMENT

Time of Estimation	Functional Grade									
On Discharge ..	I (17)*	II (126)								III (24)
First Assessment	I II	I	I	II	II	II	III	III	III	III
Second Assessment	I II	I	II	II	II	III	III	III	III	III
Third Assessment	I II	I	II	II	III	III	III	III	III	III
No. of Cases ..	9 8	35	13	45	12	11	10	6	18	6

\* Numbers of patients shown in brackets.

### Disease Activity

Although 55 per cent. of the patients remained in the same grade of disease activity at the three follow-up assessments, this figure does not indicate a degree of stability comparable with that found in respect of functional capacity. A large number of patients remained within the wide limits used to define the grade "moderately active". 37 (15 per cent.) remained inactive throughout the three assessments, showing that half of the 29.2 per cent. of patients who were inactive at the third assessment had been active at one of the previous assessments. Only seven out of 28 patients rated as

TABLE IV  
VARIATIONS IN FUNCTIONAL STATUS BETWEEN DISCHARGE AND  
THE THIRD ASSESSMENT IN 247 PATIENTS

Discharged in Grade I (30)																
Grade at First Assessment	I				II				III				IV			
	(15)				(13)				(1)				(1)			
Grade at Second Assessment	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
	(12)	(2)	(1)	—	(2)	(9)	(1)	(1)	—	(1)	—	—	—	(1)	—	—
Grade at Third Assessment	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
	(9)	(3)	(1)	—	(1)	(1)	(8)	—	—	(1)	—	—	—	(1)	—	—
	—	—	—	—	—	—	—	(1)	(1)	—	—	—	—	—	—	—
	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Discharged in Grade II (160)																
Grade at First Assessment	I				II				III				IV			
	(58)				(81)				(21)				(Nil)			
Grade at Second Assessment	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
	(43)	(15)	—	—	(7)	(59)	(14)	(1)	—	(5)	(11)	(5)	—	—	—	—
Grade at Third Assessment	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
	(35)	(8)	(2)	—	(5)	(1)	(45)	—	—	(4)	—	—	—	(1)	(10)	(2)
	—	—	—	—	—	(12)	(11)	(3)	—	—	(1)	(3)	—	—	—	—
	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Discharged in Grade III (56)																
Grade at First Assessment	I				II				III				IV			
	(5)				(15)				(31)				(5)			
Grade at Second Assessment	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
	(3)	(2)	—	—	(2)	(9)	(4)	—	(1)	(3)	(23)	(4)	—	—	(1)	(4)
Grade at Third Assessment	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
	(2)	(1)	(2)	—	(1)	(6)	(3)	(2)	(1)	(2)	(1)	—	—	—	—	—
	—	—	—	—	—	—	—	—	—	—	(18)	(1)	—	—	(1)	—
	—	—	—	—	—	—	—	—	—	—	(4)	(3)	—	—	—	(4)

NOTE: One case was discharged in Grade IV and was placed in Grade III at each of the later assessments.

inactive on admission remained inactive throughout the period of the survey, indicating that less than 3 per cent. of the whole group showed no signs of activity at any examination. No case remained very active over the three assessments and no case classed as inactive at any time ever became very active.

#### Characteristics of the Main Types

When the functional course was examined in

detail, it was found that patients could be divided into four main groups:

- (1) 46 cases remained in functional Grade I at all three assessments.
- (2) 102 cases remained in Grade II or moved between Grades I and II, indicating the retention of a reasonable degree of functional efficiency.
- (3) 50 cases remained in Grades III and IV at the three assessments, representing the more chronically disabled.



- (4) The remaining cases showed greater changes in functional capacity: 39 moved downwards from Grades I or II into Grades III or IV, and nine moved upwards from Grades III or IV into Grades I or II.

The 46 cases with the most favourable outcome were examined to see whether they could be distinguished from those with a less favourable prognosis. Table VI shows a comparison in respect of certain features of this group with the most disabled group represented by those found in Grades III or IV at the last two assessments.

The Table confirms the favourable prognostic significance of admission to hospital within one year of the onset of symptoms. All cases who were classed as having run a rapidly progressive course were admitted within one year of the onset. Nineteen of these patients were placed in Grade I at all three assessments after discharge, accounting for 41 per cent. of the group ultimately running the most benign course. The other features examined appear to be of less significance. In particular, E.S.R. on admission and age at onset show the least close relationship with subsequent progress. It is of interest to note that a proportion of patients with some of the less favourable prognostic features, such as duration of disease over 5 years before admission, insidious onset and slowly progressive course, and moderate to marked functional impairment on admission, proved capable of attaining and remaining in Grade I.

#### Functional Capacity and Disease Activity

When functional capacity is related to disease activity, it becomes obvious that ability to perform

all normal duties may be retained even when signs of activity are present. At the second assessment, for example, just under 50 per cent. of the cases in Grade I were assessed as inactive. However, in Grade II only 20 per cent. were inactive, and in Grades III and IV only 17 per cent. When functional capacity and disease activity were compared to see how many of the 46 patients who remained in functional Grade I throughout the three assessments were also inactive at those assessments, it was found that only eighteen filled this double qualification; thus only 7 per cent. of the 247 patients had suffered no impairment of function and had shown no evidence of disease activity since discharge from hospital.

#### Discussion

An analysis of the functional status and signs of disease activity in a group of patients with rheumatoid arthritis, at intervals after discharge from hospital, gives no information as to the course pursued by the individuals making up the group. Conclusions drawn from such a study only indicate general trends and give little help in forecasting the course in a particular case. For this reason an analysis of fluctuations in functional status and signs of disease activity in each patient was considered essential if a true picture of the course of this disease was to be provided. It becomes apparent from the results now presented that there is a general tendency for patients to maintain approximately the same functional level over fairly long periods after treatment in hospital. The two main groups of patients are those who fluctuate between the two upper functional grades and those who become and

TABLE VI  
COMPARISON OF INCIDENCE OF CERTAIN FEATURES IN PATIENTS WITH  
LITTLE IMPAIRMENT OF FUNCTION AND IN THOSE SEVERELY DISABLED

Clinical Particulars		46 Cases in Grade I at Assessments 1, 2, and 3		70 Cases in Grades III and IV at Assessments 2 and 3	
		No.	Per cent.	No.	Per cent.
Duration of Disease (yrs)	Under 1 .. ..	26	57	10	14
	1-5 .. ..	13	28	20	39
	Over 5 .. ..	7	15	40	57
Age at Onset (yrs) .. ..	0-39 .. ..	19	41	28	33
	40-59 .. ..	20	44	39	56
	60 and Over .. ..	7	15	8	11
Type of Course .. ..	Rapidly progressive ..	19	41	2	3
	Other types .. ..	27	59	68	97
Functional Capacity on Discharge .. ..	Grade I .. ..	9	20	3	4
	Grade II .. ..	35	76	31	44
	Grades III and IV ..	2	4	36	52
Haemoglobin on Admission .. ..	Under 80 per cent. ..	14	30	31	44
	Over 80 per cent. ..	32	70	39	56
Erythrocyte Sedimentation Rate on Admission (mm./hr) .. ..	Under 20 .. ..	11	24	11	16
	20-60 .. ..	26	57	37	53
	Over 60 .. ..	9	19	22	31

remain more severely disabled. With the passage of time, a small number of patients who have initially run a favourable course drift into the more disabled group. There is little evidence that those patients running the most benign course can be regarded as cured. Even of those showing no functional impairment throughout the period of observation, about 50 per cent. continue to show some signs of active disease. Only 7 per cent. of patients in Grade I at all three assessments after discharge were also rated as inactive at each of these examinations. It has often been stated that rheumatoid arthritis is a disease which tends to become inactive or "burnt out" in its later stages. No support for this contention has emerged from this investigation. A high proportion of those patients who had become severely disabled over the years continued to show signs of active disease. The majority of the group were rated as moderately active at every examination. This is by no means incompatible with unimpaired function.

A comparison of the incidence of certain features in patients with minimal disability and in those severely disabled has confirmed the relatively good prognosis of patients admitted within one year of the onset of symptoms, particularly if the disease has run a progressive course up to the time of admission to hospital. Other features such as age at onset, and haemoglobin and erythrocyte sedimentation rate on admission, seem to have much less bearing on the subsequent course of the disease.

### Conclusions

(1) There seems to be a general tendency for cases to remain at approximately the same functional level after treatment in hospital. The two main groups of patients are made up of those who fluctuate between a very little and moderate, but not incapacitating, disability, and those who become and remain severely disabled. As time goes on, a small proportion of cases from the more favourable group drifts into the disabled group.

(2) There is little evidence to suggest that patients running the most benign course can be regarded as cured. Of those showing no disability throughout the period of observation, half continued to show signs of disease activity. Only 7 per cent. of the total number of patients had retained full functional capacity and shown no signs of disease activity following discharge from hospital.

(3) A high proportion of those who were severely disabled still showed signs of disease activity. There was no evidence that any of these cases had "burned themselves out".

(4) The group with the best prognosis comprised

patients who had run a progressive course since the onset and who were admitted to hospital within one year.

### Summary

Analysis of functional status and disease activity in a group of patients with rheumatoid arthritis at intervals after discharge from hospital gives no information as to the course pursued by individual patients. The present communication comprises a detailed study of the types of course pursued by 247 patients with the purpose of discovering whether an appreciable number of patients shows a tendency towards permanent recovery or permanent disablement. The following conclusions have been reached:

(1) There appears to be a general tendency for patients to remain at approximately the same functional level for fairly long periods after treatment in hospital. 56 per cent. of the patients remained in the same functional grade at the three assessments after discharge, and 79 per cent. remained either in Grades I or II or in Grades III or IV. As time goes on a small proportion of cases from the more favourable group drifts into the disabled group.

(2) There is little evidence to suggest that patients running the most favourable course can be regarded as cured. Of those without disability throughout the period of observation, half continued to show signs of disease activity. Nor is there any evidence that in severely disabled patients the disease has "burned itself out". A high proportion continued to show signs of activity.

(3) The group with the best prognosis consisted of patients who had run a progressive course since the onset of symptoms and had been admitted to hospital within one year of the onset.

During the period when this work was done, the Rheumatic Unit was in receipt of grants from the Nuffield Foundation, the Medical Research Council, and Boots Pure Drug Company, Limited.

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### Variations dans l'évolution de l'arthrite rhumatismale

#### RÉSUMÉ

L'analyse périodique de l'état fonctionnel et de l'activité morbide d'un groupe de rhumatisants après leur sortie de l'hôpital donne peu de renseignements sur l'évolution des cas individuels. La communication présente offre une étude détaillée des types évolutifs de l'arthrite rhumatismale dans 247 cas; on s'y efforce de trouver si un nombre appréciable de ces cas évolue vers la guérison permanente ou une incapacité permanente.

On est arrivé à des conclusions suivantes:

(1) En général, les malades tendent à se maintenir à un niveau fonctionnel à peu près constant pendant des périodes assez prolongées après leur sortie de l'hôpital. Trois évaluations après le renvoi de l'hôpital ont montré que 56% des malades se maintenaient dans le même groupe fonctionnel et que 79% demeuraient soit dans le Grade I ou II soit dans le Grade III ou IV. Avec le temps, une petite proportion des cas du groupe favorable passe au groupe des infirmes.

(2) Rien n'indique qu'un malade dont l'arthrite suit un cours très favorable peut être regardé comme guéri. La moitié de ceux sans signes d'incapacité continuaient à accuser des signes d'activité morbide pendant toute la période d'observation. On ne trouve pas, non plus, que la maladie "s'éteint" chez ceux qui souffrent d'une sévère incapacité, car beaucoup d'entre eux accusent des signes d'activité morbide.

(3) Le groupe avec le meilleur pronostic consistait de malades avec une évolution progressive dès le début et admis à l'hôpital en dedans d'un an du début.

#### Variaciones en la evolución de la artritis reumatoide

##### SUMARIO

El análisis del estado funcional y de la actividad mórbida de un grupo de enfermos con artritis reumatoide

a intervalos de tiempo después de su salida del hospital ofrece poca información sobre la evolución de los casos individuales. La comunicación presente ofrece un estudio detallado de los tipos evolutivos de la artritis reumatoide en 247 casos; se trata aquí de hallar si un número apreciable de estos casos camina hacia una cura permanente o una invalidez permanente. He aquí las conclusiones:

(1) De una manera general los enfermos tienden a mantenerse a un nivel funcional aproximadamente constante durante períodos prologados después de haber quitado el hospital. Tres valoraciones después de darles de alta muestran que un 56% de los enfermos se mantiene en el mismo grupo funcional y que un 79% queda sea en el Grado I o II y en el Grado III o IV. Con el tiempo una pequeña proporción de los casos del grupo favorable pasa al grupo de los incapacitados.

(2) No hay datos indicando que un enfermo, cuya artritis sigue un curso muy favorable, puede considerarse curado. La mitad de los que no acusaron signos de incapacidad durante todo el período de observación, siguieron mostrando signos de actividad mórbida. Tampoco se comprobó que la enfermedad "se apaga" en los severamente incapacitados, ya que muchos acusaron signos de actividad mórbida.

(3) El grupo con el mejor pronóstico consistió de enfermos con una evolución progresiva desde el comienzo de la enfermedad y hospitalizados dentro de un año.

## ANKYLOSIS OF THE FINGER JOINTS IN RHEUMATOID ARTHRITIS

BY

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The ordinary manifestations of rheumatoid arthritis are well known and readily recognized. They are subject to wide variations and, as they deviate farther from the conventional picture, diagnosis becomes difficult, doubtful, or even impossible. The aetiology is unknown and proof of diagnosis is lacking. Even the proposed diagnostic criteria for rheumatoid arthritis (Ropes, Bennett, Cobb, Jacox, and Jessar, 1957) have not completely eliminated the difficulty, although they have made greater uniformity of classification possible. Under such circumstances, doubtful cases conforming to some diagnostic criteria but not to others are of considerable interest and often worthy of detailed study. Bony ankylosis of joints is a characteristic result of rheumatoid arthritis in a small proportion of cases, but it is non-specific for the disease. Several cases in which ankylosis of the finger joints has occurred or has been an outstanding feature have been observed which seem worthy of further attention and will be described here. In two such cases, ankylosis of the interphalangeal joints of the fingers were observed in long-standing, generalized, and severely crippling rheumatoid arthritis. These

cases are described briefly for comparison. Two other cases, however, have been followed for several years, one through a period of soft tissue inflammation and bone destruction, progressing into ankylosis. The trouble with the fingers has been the outstanding complaint. No other joints have been involved, general health has not been impaired, and since the inflammation has subsided, immobility of the fingers has been the only complaint.

### Case Reports

**Case 1**, a woman aged 52, entered the City Hospital in 1933. Her hospital record has been lost so that the clinical story is not available in detail. She had then had generalized rheumatoid arthritis for some years and was bedridden and completely handicapped. According to diagnostic criteria she was classified as a case of definite rheumatoid arthritis. According to the therapeutic criteria adopted by the New York Rheumatism Association and the American Rheumatism Association (Steinbrocker, Traeger, and Batterman, 1949), she was classified as "Stage IV Class IV", because of osteoporosis, cartilage and bone destruction, muscle atrophy, ulnar deviation, and bony ankylosis.

The hands show little deformity (Fig. 1). The wrists



Fig. 1.—Case 1, hands, showing slight swelling of wrists, ulnar deviation of fingers of right hand, and flexion of right forefinger and left little finger. Loss of transverse creases of the skin of the backs of the fingers is noticeable. The finger nails are normal.



seem to be slightly swollen, and there is obvious ulnar deviation of the fingers of the right hand, the fingers are straight except for slight flexion of the right forefinger and the left little finger, and the skin of the fingers of the right hand is particularly smooth with loss of the normal transverse creases over the proximal joints. These creases have completely disappeared over the distal joints and the fingers here seen to be constricted. The nails are normal.

Radiographs of the hands (Fig. 2) show marked demineralization of the bones, particularly around the

wrists and metacarpophalangeal and interphalangeal joints of both hands. The metacarpal bones of the wrists have lost their individual outlines and have been fused into one bony mass. The joint spaces between them and the carpal bones have completely disappeared and are diminished between them and the bones of the lower arm. All the metacarpophalangeal joints show subluxation with destruction of the proximal phalanges. The fingers of the right hand show ulnar deviation. All the interphalangeal joints, save only the distal joint of the left little finger, show complete bony ankylosis.



Fig. 2.—Case 1, postero-anterior radiographs, showing bony ankylosis of all finger joints and subluxation of the metacarpophalangeal joints. The bones of the wrist are fused and ankylosed to the radius and ulna and metacarpal bones in both hands. There is also generalized demineralization.

There was also demineralization and severe loss of joint space of the right knee and condensation of bone and loss of joint spaces in both hips.

This woman had had severe generalized rheumatoid arthritis for many years resulting in complete disability and invalidism. One outstanding feature of the disease in her case was ankylosis of all finger joints.

Case 2, a woman aged 42, was an in-patient from April to December, 1936, because of severe generalized rheumatoid arthritis of long duration. The disease had begun 8 years before with arthritis of the feet, and this had spread to involve the hands, shoulders, knees, and elbows. The pain at times was severe and stiffness developed. She became so disabled that she could not walk and had been confined to a wheel chair for the last 7 years. On admission there was marked limitation of motion of nearly all of her joints and complete stiffness

of all of the proximal joints. She was classified as a case of definite rheumatoid arthritis (Stage IV, Class IV). Attempts to correct her flexion deformities were unsuccessful and she was discharged.

The hands showed some enlargement of the wrists. There was little abnormality in the hands except that the skin over the fingers was smooth, all of the normal transverse creases over all the finger joints having been lost. The finger nails were normal.

Radiographs of both hands (Fig. 3) 8 years after the onset show demineralization of bones particularly marked in the phalanges. There is bone absorption of the carpal bones, worse in the right wrist, with fusion to each other, the metacarpal bones, and the lower arm bones. Subluxation is seen in most of the metacarpophalangeal joints. All the interphalangeal joints, except the joints of the right index and middle fingers, are the seat of bony ankylosis.

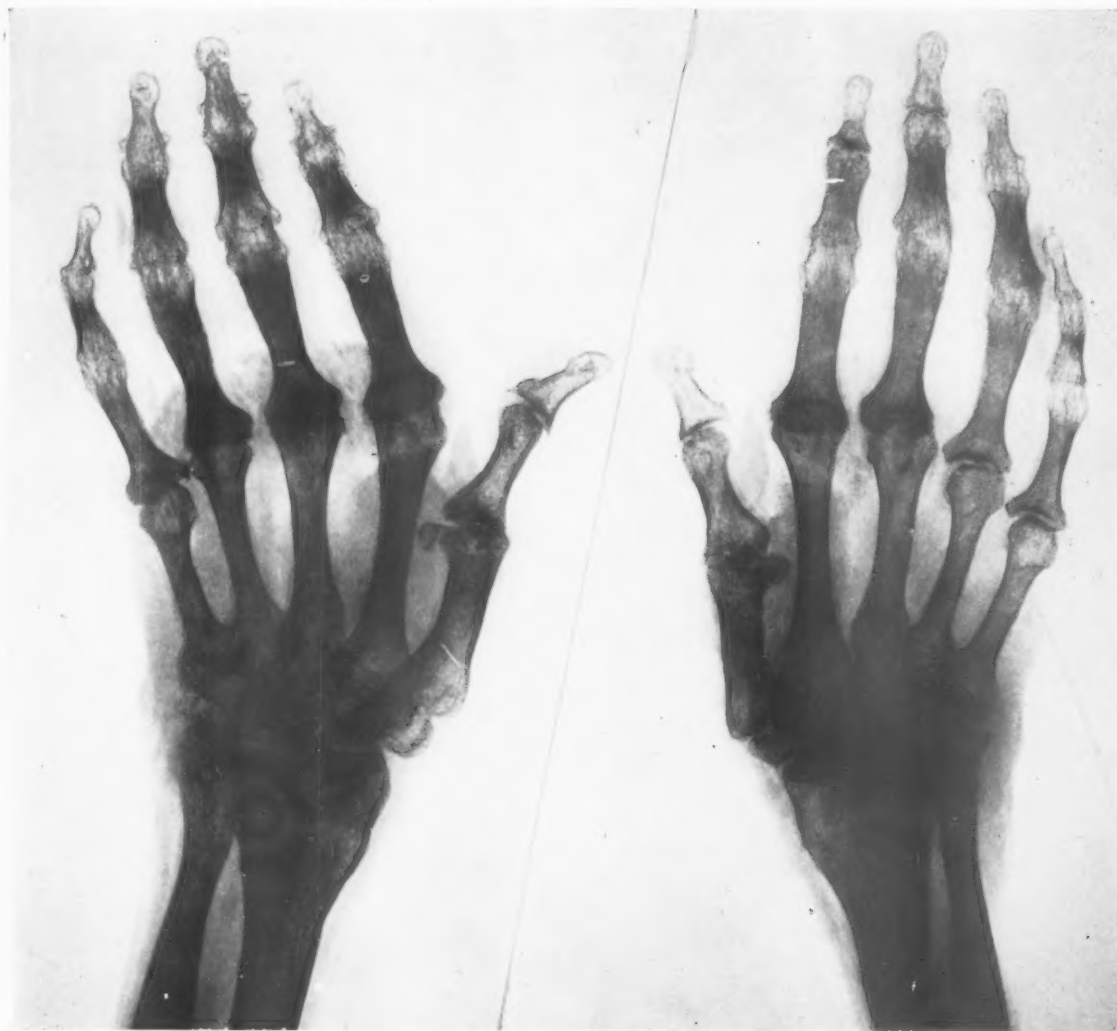


Fig. 3.—Case 2, postero-anterior radiographs of both hands 8 years after onset, showing demineralization of bones which is particularly marked in the phalanges. Absorption of the carpal bones is seen, which is more marked in the right wrist with fusion to each other, to the metacarpal bones, and to the radius and ulna. Most of the interphalangeal joints show bony ankylosis.

This woman had had severe generalized rheumatoid arthritis for 8 years, resulting in complete disability and invalidism. One outstanding feature of the disease in her case was ankylosis of nearly all finger joints.

**Case 3, a woman aged 50,** was first seen in March, 1947. Her disease had started 11 years before, at the age of 39, with swelling and pain in her hands. Limitation of motion in the fingers had been noted shortly afterwards and this had progressed so that in 1945 they had become stiffened, but after this the pain and swelling had disappeared. Pains in the feet had begun in 1940, 7 years before her first visit to hospital. They had persisted and increased in severity and had been associated at times with tenderness and swelling. For several years she had had pain in the right wrist, shoulders, hips, and knees. Her general health was fairly good but she slept poorly. Despite a poor appetite she had gained 15 lb. in 3 years. She kept her house warm, felt worse in rainy and damp weather, and had frequent chilly and nervous spells. She had been treated with innumerable hip shots, short-wave diathermy treatments, high colonic irrigations, and aspirin, and repeatedly told that she had

arthritis. Menses became irregular in 1945, at the age of 47.

Physical examination was negative except for the fingers. They were slightly flexed in the right hand and the joints were obviously ankylosed in the proximal joints. In the left hand motion was present but restricted. All the other joints seemed normal.

She was next seen in January, 1948, with dermatitis medicamentosa, which cleared up after 4 months of treatment. At this time the erythrocyte sedimentation rate was 28 mm. Hg/hr. She was next seen at her own home in June, 1952, when she said that the pain had gradually become worse so that she had finally become bedridden. She went on a complete fast for 21 days, then ate salads and fruits for several weeks and again fasted for 27 days. She lost 40 lb. in weight during this time, and the joint swelling and pain disappeared and she felt much better. The condition of her fingers was the same, however, except that the entire left little finger had become completely stiffened.

She was free of all complaints and her physical examination was negative except for her joints when she was seen in 1957 and 1958. In 1958 when she clenched her

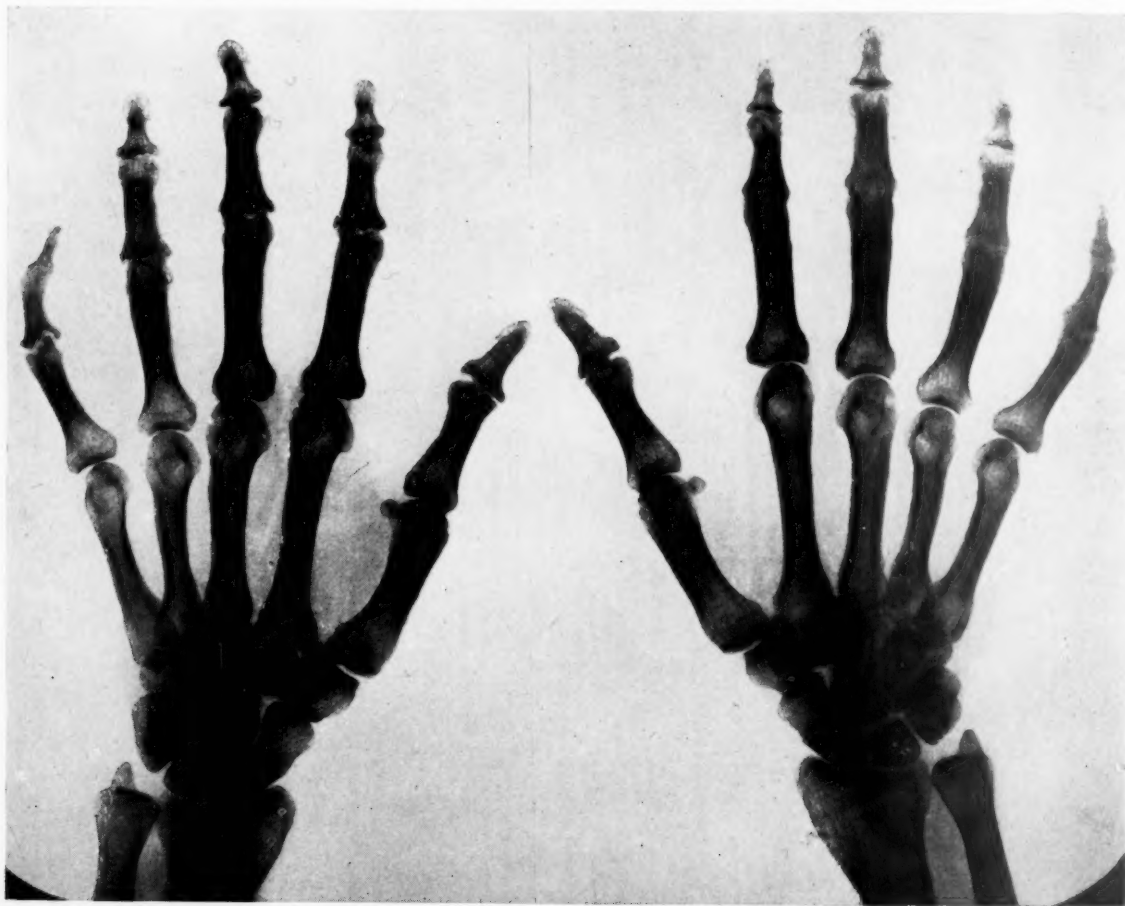


Fig. 4.—Case 3, radiographs of both hands in 1947, 11 years after onset, showing complete ankylosis of all proximal and fifth finger distal joints of the right hand. In the left hand the distal joint of the little finger is ankylosed, the proximal joints show bone destruction and alteration of joint surfaces, which is most marked in the fifth finger. Other bones and joints are normal.

fists, the metacarpophalangeal joints flexed at right-angles, but the proximal interphalangeal joints remained extended in the right hand and showed very little flexion in the left. Radiographs of the right shoulder, elbow, knee, ankle, and feet, and of the pelvis including the hips were normal.

Clinical laboratory investigations were made in 1947, 1948, 1953, 1957, and 1958. The red blood count was 3,360,000 cells per cu. mm. in 1957, but was otherwise normal, as was the haemoglobin content, white blood cell count, and serum uric acid. The erythrocyte sedimentation rate varied from 28 to 47 mm. Hg/hr by a modified Westergren method. Serological tests in September, 1957, showed latex-fixation test positive in 1/320 dilution, Heller F II test positive 1/7,000 dilution, and Waaler-Rose fixation test positive 1/1,024 dilution. Similar results were obtained in January, 1958.

This patient was considered to have rheumatoid arthritis Class IV, Stage I.

Fig. 4 shows an antero-posterior radiograph of both hands taken in 1947. Both wrists and all the metacarpo-

phalangeal joints are normal. In the right hand, the proximal interphalangeal joints of the fingers and the distal joint of the little finger are ankylosed. The distal joints of the other three fingers and the thumb are normal. In the left hand the distal joint of the little finger is ankylosed, and the proximal joint is abnormal in that the joint surfaces are irregular and saw-toothed because of irregular bone destruction. The other joints have a slightly similar but not nearly so advanced appearance. Radiographs in 1953 and 1957 showed no change except that ankylosis with stout bony fusion had occurred by 1953 in the proximal joint of the left little finger.

Fig. 5 shows lateral radiographs of each finger taken in 1953. Complete fusion is seen of all joints in both little fingers and of the proximal joints of the fingers of the right hand. All signs of joint lines or joint spaces have been obliterated. The proximal joints of the three fingers of the left hand showed a marked antero-posterior enlargement of the proximal ends of the middle phalanges, giving a cup-shaped appearance of the joint surface with rounded spurs. The distal joints of the first three

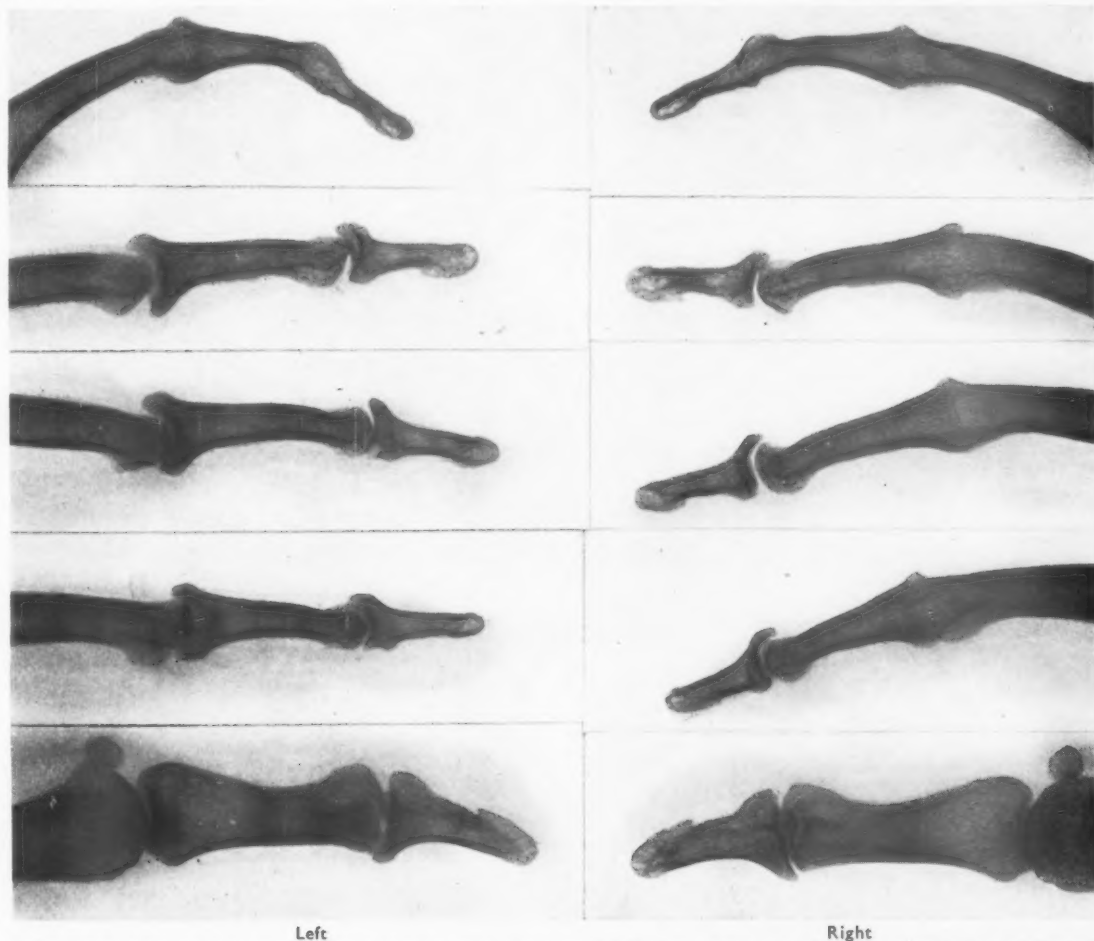


Fig. 5.—Case 3, lateral radiographs of the fingers 17 years after onset showing complete fusion of all the joints in both little fingers and in the proximal joints of the other three fingers of the right hand. The proximal joints of the first three fingers of the left hand show marked antero-posterior enlargement of the proximal ends of the middle phalanges. Spurs are seen on the posterior surface of the distal joints of the first three fingers of each hand similar to those seen in Heberden's nodes.



fingers all show marked antero-posterior enlargements arising from the dorsal aspect of the proximal end of each of the distal phalanges which resemble those seen in Heberden's nodes (Stecher and Hauser, 1948, 1954). Both thumbs are normal.

Radiographs taken in September, 1957, showed no alteration. Radiographs of both feet, right ankle, right knee, both hips and pelvis, right shoulder, right elbow, both wrists, and all metacarpophalangeal joints showed no sign of arthritic disease or other abnormality. Radiographs of the chest show normal heart and lungs.

Although the distribution of the joint disease is unusual and the lack of constitutional symptoms is surprising, this patient is considered to be a case of rheumatoid arthritis, because of the ankylosis, the consistently elevated sedimentation rate, and the positive agglutination tests. Her disease is now in complete clinical remission.

**Case 4, a woman aged 56,** was seen in 1949 because of arthritis. She had been completely well until 3 years before when she had noted swelling and soreness of the first two fingers of the right hand. Radiographs taken 2 years later had shown fusiform soft tissue swelling of the right index and middle fingers, loss of joint space, and irregularity with destruction of the bone ends. Slight changes were apparent in the ring finger. All the other joints in the fingers and wrists of both hands were normal. The process had progressed slowly involving other fingers, until all the proximal interphalangeal joints had become enlarged, tender, and partially stiffened. The patient had at different times complained of sore hands, neck, elbows, shoulders, and a toe, but no enlargement, deformity, or dysfunction had developed. Her general health was good. She had lost no weight. She had had

much conventional therapy, besides lamp treatments, bee-sting therapy, and hot baths at Hot Springs, Arkansas, and had spent 3 months in Florida without relief. Her family history was negative, in that her parents, five brothers, and sisters had had no joint disease of any kind.

Physical examination was negative except for the fingers, which showed fusiform enlargement of all of the interphalangeal joints including the thumbs. The skin was smooth and shiny, most of the normal wrinkling being decreased or absent over the backs of the distal joints and the proximal joints of the left little and ring fingers and the right index and little fingers and both thumbs. The appearance of the other joints and the skin over the metacarpophalangeal joints and the wrists was completely normal.

The diagnosis at this time was doubtful. Despite the typical appearance of rheumatoid arthritis of the fingers, the diagnosis of osteo-arthritis of the fingers was made because of absence of other joint disease 3 years after onset and because of her normal health and normal laboratory findings.

The patient was next seen in December, 1951, when she was still complaining of stiff and painful wrists, hands, and fingers. Since her previous visit, she had had diathermy treatments and paraffin baths for one year without relief. This was followed by cortisone for 20 days, which gave her relief from pain in the wrists and neck, improved her appetite and digestion, and gave her a feeling of well-being, but oedema developed. Acetylsalicylic acid and codeine had upset her stomach and had to be discontinued. Gold therapy was suggested but not used. At this visit she was emotionally disturbed, easily upset, wept readily, and complained of frequent headaches. These symptoms were attributed



Fig. 6.—Case 4, 3 years after onset; the hands appear normal except for fusiform enlargement of the proximal joints of the fingers and loss of transverse creases of the skin over the terminal joints of the little fingers and thumbs.

largely to the illness and disability of her husband. Physical examination at this time was negative except for complete ankylosis of all proximal interphalangeal joints.

Little change in her condition was noted on visits in 1952, 1955, and 1957. Cortisone had been started again but this was stopped in 1953 because she had developed a moon face and buffalo hump. She then had 36 gold shots without effect, and since 1953 she has had little or no therapy. Her spirits, her appetite, and her general outlook on life have improved, and despite her bedridden husband whom she cares for at home, she seems happy, contented, and well, with no complaints except a stiffness of the fingers which does not bother her.

Physical examination in 1955 and again in 1958 revealed no abnormality whatsoever in the spine, shoulders, elbows, hips, knees, ankles, or feet. Motion of both wrists were limited to about half the normal range; the interphalangeal joints were fixed, of course, but the other joints of the hand functioned normally.

Laboratory investigations carried out in 1949, 1951, 1952, 1955, 1957, and 1958, showed normal red blood cell count, white blood cell count, haemoglobin level, and haematocrit. The red blood cell sedimentation rate was 21, 22, and 26 mm. Hg/hr (corrected) until 1952. In 1955 and 1958 the rate was 9 and 3 mm. respectively.

The latex-fixation test, Heller F II test, and Waler-Rose test were negative on May 21, 1957, and January 20, 1958.

If the diagnosis of rheumatoid arthritis is accepted in this case, it can be considered as Class IV, Stage I. The diagnosis is very doubtful, however, because the erythrocyte sedimentation rate has been normal or only slightly elevated, the serological agglutination tests have been negative, and no joint changes have been recognized except those of the hands and the wrists. Except for the ankylosis the joints have not been typical of rheumatoid arthritis. The patient's subjective symptoms can be accounted for by her personal problems.

The progress of the disease in this case can best be followed by examination of photographs and radiographs. Photographs of the hands taken on the first visit in 1949, 3 years after onset (Fig. 6), show fusiform enlargements of the fingers as described above. Radiographs of both hands (first taken in 1948, 2 years after onset) showed, besides demineralization, soft tissue swelling about the proximal interphalangeal joints, decrease in joint space, and destruction of the joint surfaces of the index and middle fingers of the right hand. Radiographs of both hands repeated in May, 1949, (Fig. 7) show extension of the process. The proximal ends of the middle interphalangeal joints are broadened, roughened, and eroded, indicating loss of bone substance.

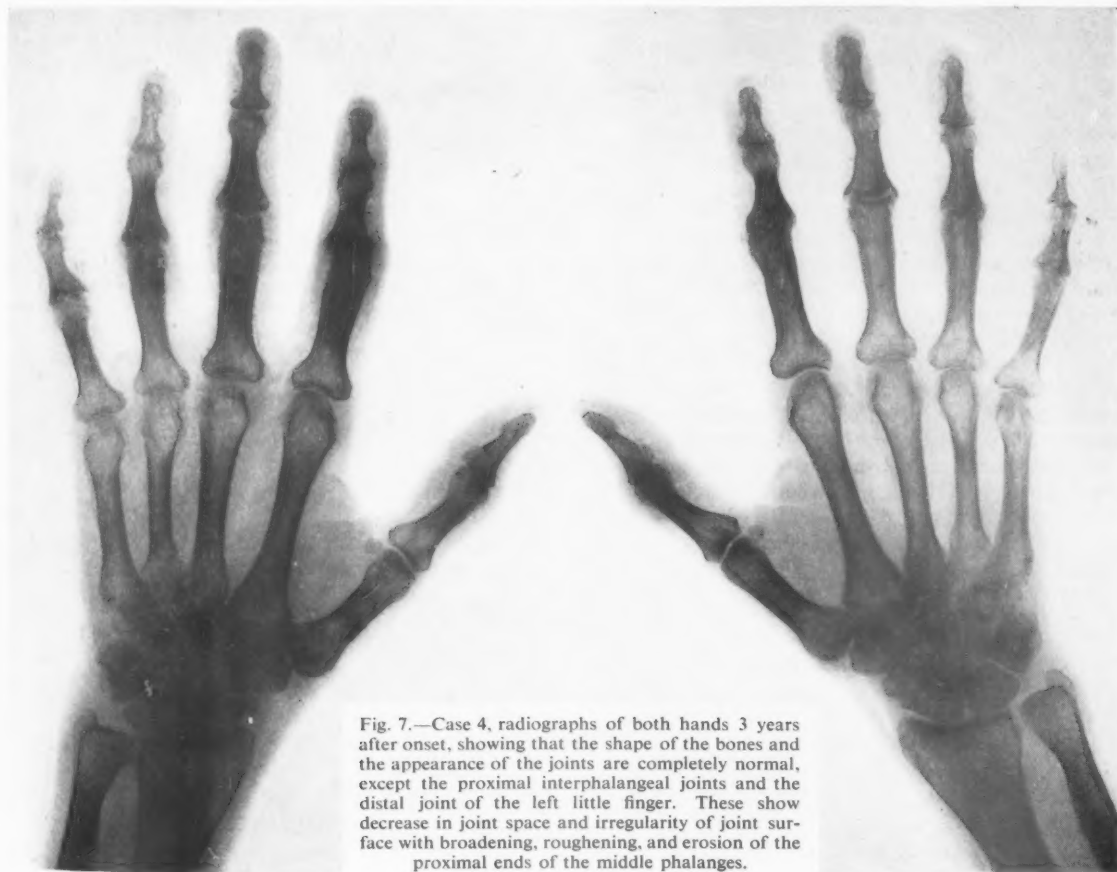


Fig. 7.—Case 4, radiographs of both hands 3 years after onset, showing that the shape of the bones and the appearance of the joints are completely normal, except the proximal interphalangeal joints and the distal joint of the left little finger. These show decrease in joint space and irregularity of joint surface with broadening, roughening, and erosion of the proximal ends of the middle phalanges.

A similar process is suspected in the terminal joints of both little fingers and thumbs. The other joints of the hands and wrists are not affected. Lateral views of the fingers of the right hand taken in May, 1949 (Fig. 8), show irregularity of joint line and erosion of bone substance. There is bone production at the anterior and posterior profiles of the proximal ends of the middle phalanges.

Radiographs of both hands taken in July, 1955, 9 years after onset, showed a definite destructive process of the distal joints of the left thumb and left little finger but all of the proximal interphalangeal joints of the fingers were then completely ankylosed. Photographs at this time showed the skin of the fingers to be smooth and shiny with no remnants of the transverse creases normally present over the joints. The patient could not clench her fist because of the immobility of the proximal finger joints.

Lateral radiographs of all the fingers taken in July, 1955 (Fig. 9, opposite), show obliteration by bony ankylosis of all the proximal interphalangeal joints of the fingers, and the distal joints of the right little finger and the right thumb. No evidence of a joint space or joint line remains, the position of the joint being identified by smooth continuous fusiform enlargement of the bones. Spurs are now seen on the dorsal aspects of the proximal ends of the distal phalanges of all the fingers, except the right little finger, which are typical of those seen in Heberden's nodes.

The most recent radiographs taken in January, 1958, 12 years after the onset (Fig. 10, overleaf), show complete bony ankylosis of all of the proximal interphalangeal joints of both hands and the distal joint of the right little finger and thumb. The metacarpophalangeal joints are normal, except that of the left little finger which shows a cup-shaped deformity in the proximal end of the middle phalanx with erosion of the distal surface and irregularity of the proximal surface. Changes in the wrist show decrease in size of the proximal bones of the wrist, irregularity of joint surfaces between them and the radii and ulnae, and condensation of bone of the joint surfaces. The joint spaces are well preserved. The irregularities of mineralization are due to technical difficulties in making the photographic prints.

Thus, despite a destructive joint disease resulting in a complete bony ankylosis studied for 10 years, the diagnosis of rheumatoid arthritis is doubtful because of the sharp localization of the disease, the absence of constitutional symptoms, the only slightly elevated erythrocyte sedimentation rate, and the negative serological tests.

### Discussion

Case histories, clinical records, and iconographic descriptions are given of four women, each of whom suffered from ankylosis of the interphalangeal joints of the fingers. The first two are cases of severe generalized rheumatoid arthritis. These patients had disease of long standing, with wide-



Fig. 8.—Case 4, lateral views of the fingers of the right hand 3 years after onset, showing most marked changes in the proximal joints. The joint spaces are irregular and the joint surfaces are roughened and broadened. Considerable bone destruction is visible. Spurs are seen on the distal phalanges.

spread joint damage throughout the body, and complete disablement. The patients were placed in Class IV, Stage IV, according to the classification adopted by the American Rheumatism Association. The other two cases differ from the first two in that permanent joint damage has been limited to the hands and constitutional symptoms, which were never severe, have completely disappeared. The patients seem to be in excellent health and only slightly handicapped by the changes in the hands. The third case has been classified as Class IV, Stage I, solely because some joints show complete ankylosis. Radiographic studies of the fingers show progression of the disease from a stage of fusiform enlargement and bone destruction about the proximal interphalangeal joints to the present condition when the bones are completely ankylosed

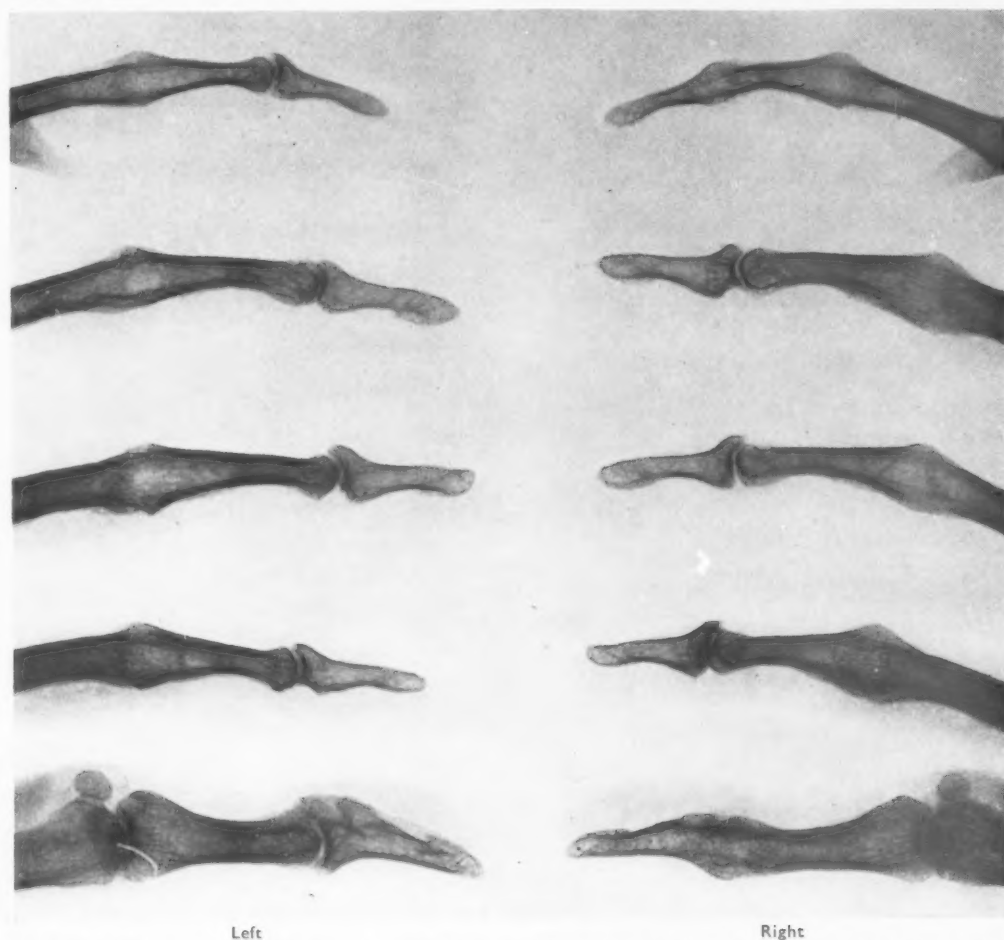


Fig. 9.—Case 4, lateral views of the fingers 7 years after onset, showing bony ankylosis of all the proximal joints and of the distal joints of the right little finger and thumb. Spurs are seen in the dorsal aspects of the proximal ends of the distal phalanges similar to those seen in Heberden's nodes.

and the fingers have regained their normal size. No other joint changes in the body are recognizable by clinical examination or by extensive radiographic survey. The diagnosis in this case is substantiated by positive serological tests on two occasions and an elevated erythrocyte sedimentation rate. A definite diagnosis is justified according to the proposed diagnostic criteria for rheumatoid arthritis, since there was at one time pain and tenderness, swelling, symmetrical involvement, radiographic changes, and a positive latex agglutination test. Despite the ankylosis, clinical activity is now minimal; the unusual aspects of the case are the very restricted distribution of joint involvement, the temporary and mild constitutional symptoms, and the complete restoration of health and activity for several years. If this patient were seen now and not carefully studied the diagnosis might easily be overlooked.

The fourth case is similar to the previous one in that the disease has been limited to the hands, and that constitutional symptoms have been mild and have now completely disappeared. In this patient the erythrocyte sedimentation rate has never exceeded 26 mm. Hg/hr, and for the last 3 years has been below 10 mm. The agglutination tests have been completely negative twice in the last year. A definite diagnosis is not so clearly justified according to the proposed diagnostic criteria. Symmetrical involvement, radiographic changes, and stiffness in symmetrical joints have been noted, but because she was not observed, during the early stages, details of her symptoms at that time are not known. The patient has been classified as Class IV because of bony ankylosis, but has been placed in the Stage I category because of her complete ability to carry on all her usual duties without handicap. She must be considered as at least a possible case





Fig. 10.—Case 4, radiograph 12 years after onset showing complete bony ankylosis of the proximal interphalangeal joints of both hands and of the distal joints of the right little finger and thumb. The metacarpophalangeal joint of the left little finger shows a cup-shaped deformity of the phalanx. Wrists show decrease in size of the proximal carpal bones.

of rheumatoid arthritis if not a probable case, but the diagnosis cannot be considered as proven.

Although discussion has been limited to a consideration of rheumatoid arthritis in these cases, there are certain additional features suggestive of degenerative joint disease. Lateral views of the fingers (Figs 5 and 9) show large spurs projecting dorsally from the proximal ends of the distal phalanges. These spurs are thick and have rounded ends suggestive of traumatic Heberden's nodes. It is unusual, however, to see six instances of traumatic Heberden's nodes in one individual as in Fig. 5. Idiopathic Heberden's nodes are usually associated with loss of joint space, greater irregularity of joint surface, and pointed spurs. Heberden's nodes with spurs as large as those shown here are always associated with considerable enlargement of the fingers, but these fingers were not enlarged in the region of the terminal joints. The carpal bones in Fig. 10 show changes in outline with loss

of substance particularly of the semi-lunar bones. The joint spaces are adequately preserved and the joint surfaces are sharp and show condensation of bone. The rest of the carpal bones are not altered. These changes are difficult to classify because they seem to differ sharply from those usually seen in the arthritic diseases. Bone seems to have been absorbed, but there is no inflammation and the causative process seems to be completely quiescent and healed. Even if the changes in the terminal finger joints and the wrists are accepted as manifestations of osteo-arthritis, the limited distribution of these changes do not justify the characterization of the condition as generalized osteo-arthritis as described by Kellgren and Moore (1952).

### Summary

Ankylosis of the phalanges without deformity is uncommon even in severe cases of rheumatoid

arthritis. Four female patients who suffered from ankylosis of the interphalangeal joints of the fingers are described in detail.

Two had severe generalized rheumatoid arthritis leading to complete disablement, but in the other two permanent joint damage was limited to the hands and the mild systemic symptoms disappeared, leaving little if any disability.

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## Ankylose des articulation digitales dans l'arthrite rhumatismale

## RÉSUMÉ

L'ankylose des phalanges sans déformation es peu commune même dans des cas sévères d'arthrite rhuma-

tismale. On décrit en détail quatre cas de femmes atteintes d'ankylose des articulations interphalangiennes des doigts.

Deux d'entre elles souffraient d'une arthrite rhumatismale généralisée et sévère menant à l'incapacité totale, mais chez les deux autres le dommage se limitait aux mains, les symptômes généraux ayant disparu avec peu ou pas d'incapacité résiduelle.

## Anquilosis de las articulaciones digitales en la artritis reumatoide

## SUMARIO

La anquilosis de las falanges sin deformidad no es común hasta en los casos graves de artritis reumatoide. Se describen detalladamente cuatro casos de mujeres con anquilosis de las articulaciones interfalangeas de los dedos.

Dos de éstas sufrieron de una artritis reumatoide generalizada y grave conduciendo a la incapacidad total, pero en las demás el daño se limitó a las manos, los síntomas generales habiendo desaparecido con incapacidad residual poca o ninguna.

## CLINICAL OBSERVATIONS WITH 16a-METHYL CORTICOSTEROID COMPOUNDS\*

### PRELIMINARY THERAPEUTIC TRIALS WITH DEXAMETHASONE (16a-METHYL 9a-FLUOROPREDNISOLONE) IN PATIENTS WITH RHEUMATOID ARTHRITIS

BY

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During the past 3 years it has been demonstrated that the substitution of a methyl radical at one or another carbon position in the steroid nucleus may cause major changes in certain physiological activities of adrenal cortical steroids. A number of methylated analogues of hydrocortisone and cortisone have been prepared and currently these are being studied both experimentally and clinically with the hope that information may be gained which will lead ultimately to the development of therapeutically superior anti-inflammatory compounds.

Hogg, Lincoln, Jackson, and Schneider (1955) and Spero, Thompson, Magerlein, Hanze, Murray, Sebek, and Hogg (1956) synthesized several methylated steroid compounds. It was determined that when a methyl radical was substituted at the second carbon position the electrolyte metabolism of corticosteroids was augmented, but if the methyl grouping was placed at the sixth carbon position instead, sodium retention and potassium loss were not increased. During 1956 and 1957 the physiological and therapeutic effects of 6a-methylprednisolone were investigated (Boland and Liddle, 1957). Biologic screening tests in animals had suggested that the analogues might possess greater anti-inflammatory potency, and perhaps a higher therapeutic index, than prednisolone (Lyster, Barnes, Lund, Meinzing, and Byrnes, 1957). Studies in human subjects revealed, however, that, while the sodium-retaining and potassium-losing activities of 6a-methylprednisolone might be less than those of prednisolone, the other metabolic effects of the two compounds were about the same when equal milligram amounts were administered. Dosage

comparison studies in patients with rheumatoid arthritis established that the antirheumatic strength of 6a-methylprednisolone was slightly greater (about 15 to 25 per cent.) than that of prednisolone (Boland and Liddle, 1957).

During 1957 Sarett and his collaborators synthesized a new family of steroid compounds containing in common a methyl grouping at the sixteenth carbon position of the steroid nucleus (Arth, Johnston, Fried, Spooner, Hoff, and Sarett, 1958). In May, 1957, 16a-methylprednisone was subjected to cursory clinical evaluation by the author, and the antirheumatic potency of the compound was compared with that of prednisolone in eleven patients with rheumatoid arthritis. As far as could be determined, the potencies of the two steroids were about equal; if differences did exist they were too small to calibrate clinically. Long-term treatment studies with 16a-methylprednisone were not pursued.

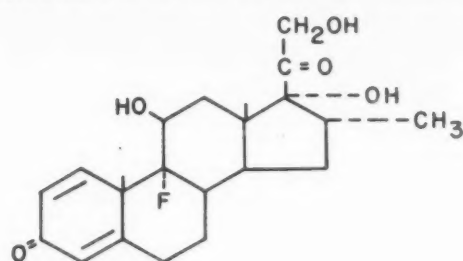
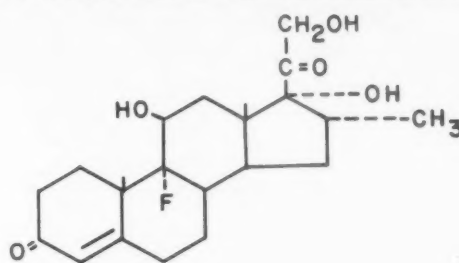
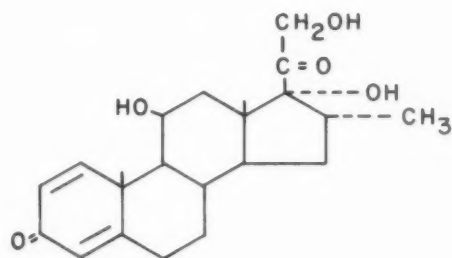
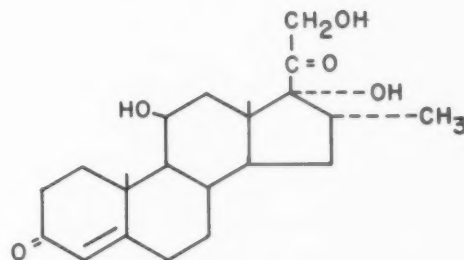
In December, 1957, four separate 16a-methylated derivatives of hydrocortisone were made available for clinical trial.† They were: 16a-methyl 9a-fluoroprednisolone, 16a-methyl 9a-fluorohydrocortisone, 16a-methylprednisolone, and 16a-methylhydrocortisone (Fig. 1, opposite). 16a-methyl 9a-fluoroprednisolone first received the generic name of "hexadecadrol", but this was later changed to "dexamethasone". Dexamethasone differs chemically from triamcinolone by having a methyl instead of a hydroxyl grouping at the 16-alpha carbon position. As yet, the three remaining analogues have not been given generic names.

Screening tests in animals for the biologic behaviour of these hydrocortisone derivatives conducted by Silber and his group (Arth, Fried, Johnston, Hoff, Sarett, Silber, Stoerk, and Winter,

\* From the Department of Medicine, St. Vincent's Hospital, Los Angeles. This study was supported, in part, by a grant from the Ahmanson Foundation.

Paper presented at the scientific session honouring Dr. Philip S. Hench on the occasion of the tenth anniversary of the discovery of the antirheumatic effects of cortisone (Rochester, Minn., October 1, 1958).

† The 16a-methyl analogues of hydrocortisone and cortisone used in this study were supplied by the Merck Sharp and Dohme Research Laboratories, Division of Merck and Co. Inc., Rahway, New Jersey.

16 $\alpha$ -METHYL, 9 $\alpha$  FLUORO-  
PREDNISOLONE16 $\alpha$ -METHYL, 9 $\alpha$  FLUORO-  
HYDROCORTISONE16 $\alpha$  METHYL PREDNISOLONE16 $\alpha$  METHYL HYDROCORTISONEFig. 1.—Structural formulae of four 16 $\alpha$ -methyl analogues of hydrocortisone.

1958), indicated that methylation at the 16- $\alpha$  carbon position produced striking changes in several physiological properties, including a decided intensification of anti-inflammatory action and an absence of sodium retention with the experimental dosages tried (Table I). Each of the compounds displayed, in varying degrees, greater physiological potency than hydrocortisone—and in the case of 16 $\alpha$ -methyl

9 $\alpha$ -fluoroprednisolone and 16 $\alpha$ -methyl 9 $\alpha$ -fluoro-hydrocortisone particularly, certain properties were tremendously enhanced by methylation at the sixteenth position. Of interest and importance was the finding that the anti-inflammatory potency of dexamethasone, as gauged by granuloma inhibition, was augmented to a much greater extent than glycogen deposition—190 times as compared with 17 times—

TABLE I  
RELATIVE POTENCIES OF CERTAIN BIOLOGIC ACTIVITIES OF 16-ALPHA METHYL CORTICOSTEROIDS  
AS DETERMINED IN ANIMALS (ADAPTED FROM ARTH AND OTHERS (1958a))

Steroid Tested	Potency Times Hydrocortisone of:			
	Thymus Involution	Granuloma Inhibition	Adrenal Atrophy	Glycogen Deposition
16 $\alpha$ -methyl 9 $\alpha$ -fluoroprednisolone (Dexamethasone) ..	400	190	700	17
16 $\alpha$ -methyl 9 $\alpha$ -fluorohydrocortisone .. ..	55	36	85	12
16 $\alpha$ -methylprednisolone .. .. .	14	12	16	5
16 $\alpha$ -methylhydrocortisone .. .. .	1.9	3	1.8	2.1
16 $\alpha$ -methylprednisone .. .. .	11	13	10	3.2



suggesting that there might be a therapeutically useful dissociation of these two effects.

#### Anti-rheumatic Potencies of 16a-Methyl Analogues of Hydrocortisone as compared with Prednisolone

The antirheumatic potency of each of the four new 16a-methylated analogues of hydrocortisone was compared with that of prednisolone (Table II). This was accomplished by transferring treatment in carefully selected patients back and forth from prednisolone to the test substance and ascertaining the milligram dosages required to maintain equivalent degrees of improvement (Boland, 1958).

Dosage comparison studies were made with dexamethasone in 21 patients. The dosage ratios of dexamethasone to prednisolone varied from 1 : 5 to 1 : 10, but in the majority the range was from 1 : 6 to 1 : 8. Thus, in this group of patients, the antirheumatic potency of dexamethasone was, on average, about seven times greater than prednisolone, per milligram. By calculation it could be considered to have roughly thirty times the potency of hydrocortisone.

The antirheumatic strength of 16a-methyl 9a-fluorohydrocortisone was found to be considerably more than that of prednisolone. In eleven patients the average was approximately three times greater.

16a-methylprednisolone exhibited greater anti-rheumatic potency than prednisolone, but the variation was fractional rather than multiple—it was roughly one-third more potent on average.

The average antirheumatic strength of 16a-methylhydrocortisone was found to be about 70 per cent. that of prednisolone. Direct comparisons with hydrocortisone yielded proportionately similar results: the doses of hydrocortisone required for equivalent improvement were approximately three times greater than for 16a-methylhydrocortisone.

#### Preliminary Therapeutic Trials with Dexamethasone\*

Since December, 1957, the clinical effects of dexamethasone have been studied in 88 rheumatoid arthritic patients. An analysis of the improvement status was made in 55 of the patients who had received the drug uninterruptedly for 3 to 5 months, and the following results were obtained:

Eleven patients, not previously treated with steroids, were given dexamethasone as initial therapy. Dosages were varied according to disease severity and ranged from 1 to 2.5 mg. per day, an effort being made to avoid rapid and dramatic improvement with excessive doses at the beginning. The pattern of response was much the same as with other effective anti-inflammatory steroids prescribed in proportionately larger milligram amounts. At analysis, the degree of improvement was gauged as marked or very marked in nine of eleven patients (Table III, opposite). The average daily maintenance dose at the end of 3 to 5 months was 1.3 mg. (range 0.8 to 2 mg.). Unwanted side-effects developed in five of the patients: asymptomatic peptic ulcers in two, facial mooning in one, and excessive weight gain in two.

Treatment was transferred from prednisolone to dexamethasone in 44 patients. The patients were divided into two groups—those who had been adequately controlled on prednisolone, and those who had not. Each of seventeen patients that had responded satisfactorily to prednisolone retained adequate control after transfer to the new drug, and at the end of 3 to 5 months the degree of improvement had advanced from marked to very marked in five patients (Fig. 2, opposite). The average maintenance dosage for dexamethasone was 1.4 mg. per day, an amount which, by calculation, was some-

\* Dexamethasone was supplied by the Merck Sharp and Dohme Research Laboratories, Division of Merck and Co. Inc., Rahway, New Jersey, under the trade name of "Decadron".

TABLE II  
ANTIRHEUMATIC POTENCIES OF 16a-METHYL ANALOGUES OF HYDROCORTISONE COMPARED TO PREDNISOLONE: BASED ON CLINICAL APPRAISALS IN PATIENTS WITH RHEUMATOID ARTHRITIS (ARTH AND OTHERS, 1958a)

Steroid Tested	Number of Patients Studied	Dosage Ratios to Prednisolone		Potency Ratios to Prednisolone	
		Range	Average	Range	Average
16a-methyl 9a-fluoroprednisolone (Dexamethasone) . .	21	1 : 5 to 1 : 10	1 : 7.3	5 : 1 to 10 : 1	7.3 : 1
16a-methyl 9a-fluorohydrocortisone . . . . .	11	1 : 2.5 to 1 : 4.2	1 : 3.2	2.5 : 1 to 4.2 : 1	3.2 : 1
16a-methylprednisolone . . . . .	7	1 : 1 to 1 : 1.7	1 : 1.3	1.7 : 1 to 1 : 1	1.3 : 1
16a-methylhydrocortisone . . . . .	12	1 : 0.6 to 1 : 1	1 : 0.7	1 : 1 to 0.6 : 1	0.7 : 1

Case No.	
1	F
2	M
3	F
4	F
5	F
6	F
7	F
8	F
9	F
10	F
11	F
Ave	

Fig.

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TABLE III  
RESPONSE TO DEXAMETHASONE AFTER 3 TO 5 MONTHS OF THERAPY IN ELEVEN PATIENTS  
NOT PREVIOUSLY TREATED WITH STEROIDS

Case No.	Sex	Disease Severity	Dosage (mg. per day)		Length of Treatment (wks)	Degree of Improvement			Adverse Effects at Analysis (Grading: 1 to 4)
			Initial	Maintenance		Degree	Adequate	Inadequate	
1	Female	Severe	2.0	1.0	15	Marked	x		Prepyloric ulcer (asymptomatic)
2	Male	Severe	2.5	1.4	16	Very marked	x		
3	Female	Severe	2.5	1.0	18	Marked	x		
4	Female	Moderately Severe	2.0	1.2	21	Marked	x		
5	Female	Moderately Severe	2.0	1.2	17	Marked	x		
6	Female	Moderately severe	2.0	1.0	14	Very marked	x		Weight gain (2) Abdominal girth (2)
7	Male	Moderately severe	2.0	1.8	14	Moderate		x	Weight gain (2) Diabetes not aggravated
8	Male	Moderately severe	2.0	1.6	20	Very marked	x		Prepyloric ulcer (asymptomatic)
9	Male	Moderately severe	2.0	2.0	21	Moderate		x	Facial mooning (2)
10	Female	Moderate	1.0	0.8	21	Very marked	x		
11	Male	Moderate	1.0	1.0	20	Marked	x		
Average .. ..			1.9	1.3	18				

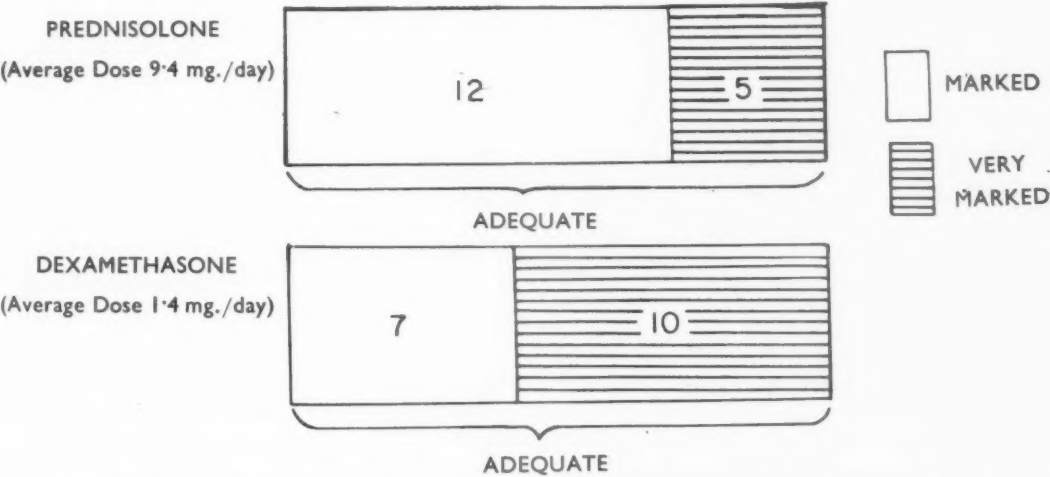


Fig. 2.—Improvement status 3 to 5 months after transfer to dexamethasone in seventeen patients adequately controlled on prednisolone.

what greater in potency than for prednisolone before transfer.

Changes in the improvement status of 27 patients who had been poorly controlled on prednisolone are shown in Fig. 3 (overleaf). This was a recalcitrant group of patients with severe or moderately severe disease, having received continuous steroid therapy for long periods. Many of them had been controlled

successfully at one time or another, but with continuation of treatment they had grown worse. Attempts were made to achieve better rheumatic control by cautiously increasing the dosages of dexamethasone to amounts exceeding those used for prednisolone, in terms of antirheumatic potency. At the end of 3 to 5 months improvement had been raised to adequate levels in more than one-third

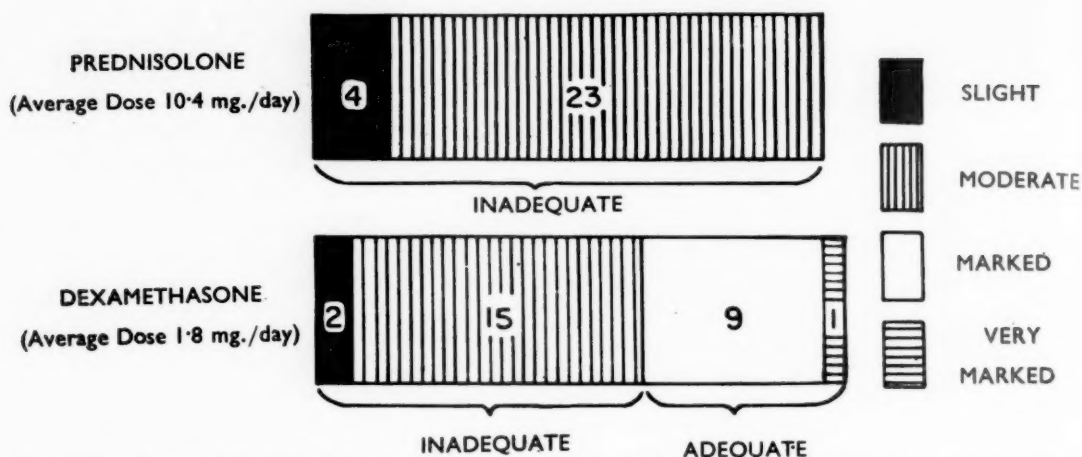


Fig. 3.—Improvement status 3 to 5 months after transfer to dexamethasone in 27 patients not adequately controlled on prednisolone.

of the group. But the total number of adverse reactions had not diminished: decreases or disappearances of such side-effects as oedema, digestive symptoms, and nervous excitation in some patients were counterbalanced by excessive weight gain, increased ecchymotic skin lesions, facial mooning, and abdominal bloating and distension in others, and by the appearance of unsuspected peptic ulcers. It may be anticipated that the overall improvement status of this obstinate group will deteriorate statistically as treatment is further prolonged.

#### Preliminary Observations of Adverse Effects from Dexamethasone

Certain general impressions regarding unwanted side-effects from dexamethasone as compared with those noted with prednisolone may be summarized as follows:

(1) The overall incidence of adverse reactions from dexamethasone appears to be about the same as of those from prednisolone when equally effective antirheumatic doses of the two drugs are given. However, certain differences in individual side-effects have been noted.

(2) Symptoms which are apparently peculiar to triamcinolone, such as headache, dizziness, fatigue, anorexia, weight loss, muscle weakness, and erythema, have not occurred during dexamethasone administration.

(3) Peripheral oedema (mild to moderate) was noted in five of 88 patients; but, in general, the tendency for salt and water retention appeared to be less with dexamethasone than with prednisolone,

and decidedly less than with hydrocortisone.

(4) None of the patients studied so far has developed hypertension or has demonstrated aggravation of pre-existing hypertension.

(5) When dexamethasone is given in doses of comparable antirheumatic strength it appears to have about the same tendency as prednisolone to promote facial mooning, supraclavicular fat pads, and hypertrichosis.

(6) The occurrence rate and the severity of ecchymotic skin lesions are just as great, and perhaps greater, with dexamethasone as with prednisolone when similarly effective antirheumatic amounts of the drugs are taken.

(7) The most common side-effects encountered to date, and certainly those which have been most objectionable to patients, are increased appetite, excessive weight gain, and the development of abdominal girth. Preliminary observations suggest that dexamethasone may promote these reactions more readily than prednisolone when equivalently effective doses are given. In some instances excessive weight gain occurred without the quickening of appetite. A number of patients observed that the increased weight accumulated predominantly about the waist. At times such increased girth appeared without substantial weight gain and without accompanying facial mooning or supraclavicular fat pads.

(8) Approximately 10 per cent. of the patients experienced abdominal distension or bloating. In some, this complaint was persistent, but it was more often transient and recurring.

(9) It would appear that dexamethasone may be administered in effective antirheumatic doses to

patients with mild or moderate diabetes mellitus without further disrupting their carbohydrate metabolism. At least this is indicated from the experience of four patients in this series with co-existing diabetes. Three of them were well maintained with doses of 1.8, 1.5, and 1.25 mg. per day, respectively, without increasing glycosuria or insulin requirement. The fourth patient, whose disease was controlled by dietary restriction alone, has noted glycosuria more often since receiving dexamethasone in dosages of 1 mg. per day than he did without steroid therapy—but, by contrast, previous trials with prednisolone and with hydrocortisone had aggravated this patient's diabetes so greatly that it had been necessary to discontinue the drugs entirely.

(10) Nervous symptoms were rarely encountered with dexamethasone in doses up to 3 mg. per day, and it would appear that the tendency towards this reaction is less than with prednisolone given in proportionately effective antirheumatic doses. None of the patients in the present series experienced mental excitation requiring either cessation of therapy or alteration of dosage.

(11) Symptoms suggesting peptic ulcer were uncommon, but the incidence of peptic ulcer during dexamethasone administration appears to be comparable to that which occurs with prednisolone, and deserves comment.

Seventy patients who had taken dexamethasone for 3 months or longer were subjected to routine upper gastro-intestinal x-ray studies. Six active peptic ulcers were detected, five of which were prepyloric in location. Four of these were entirely asymptomatic, one was mildly symptomatic, and only one was accompanied by typical ulcer symptoms. With strict ulcer management, and without discontinuing the drug or reducing its dosage, five of the six ulcers healed roentgenographically within 6 weeks. In the sixth patient a prepyloric ulcer was smaller roentgenographically after 6 weeks of treatment, but a new ulcer was detected in the duodenum. The patient was then transferred to prednisolone treatment and rigid ulcer management was continued, but after another 8 weeks neither lesion had healed and steroid therapy was withdrawn. Since it was demonstrated that dexamethasone, like other anti-inflammatory steroids, has ulcerogenic properties, antacids have been prescribed routinely with each divided dose of the drug.

### Summary

Four new synthetic analogues of hydrocortisone, containing in common a methyl grouping at the 16a-carbon position of the steroid molecule, are

being studied in human subjects. The compounds are:

- 16a-methyl 9a-fluoroprednisolone (dexamethasone: Decadron),
- 16a-methyl 9a-fluorohydrocortisone,
- 16a-methylprednisolone,
- 16a-methylhydrocortisone.

Biologic tests carried out in animals demonstrated that these compounds exhibit, in varying degrees, striking alterations of several physiological properties, including enhanced anti-inflammatory activity unassociated with corresponding disturbance of electrolyte metabolism. Preliminary observations of the effects of the four new compounds in patients with rheumatoid arthritis are summarized.

Clinical estimates of the antirheumatic potency of the compounds, as compared with that of prednisolone, were accomplished by determining the milligram dosages required to maintain similar degrees of improvement of active rheumatoid manifestations. The approximate antirheumatic potencies of the compounds, on an average, were gauged as follows:

- 16a-methyl 9a-fluoroprednisolone (dexamethasone), about seven times greater than prednisolone;
- 16a-methyl 9a-fluorohydrocortisone, about three times greater;
- 16a-methylprednisolone, approximately one-third greater;
- 16a-methylhydrocortisone, about 70 per cent. that of prednisolone.

The therapeutic efficiency of dexamethasone, one of the new methylated analogues, is now being investigated in a large group of patients with rheumatoid arthritis. This compound is the most potent antirheumatic steroid which has been synthesized to date, and is highly effective in suppressing the manifestations of rheumatoid arthritis when administered in remarkably small daily doses. However, augmented antirheumatic potency alone does not denote superiority, and these clinical trials have been too brief, as yet, to allow us to judge whether dexamethasone possesses therapeutic advantages over prednisone or prednisolone in the management of those rheumatoid arthritic patients who are suitable for long-term steroid therapy.

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**Observations cliniques sur des composés 16a-méthyl corticostéroïdes: essais thérapeutiques préliminaires de la dexaméthasone (16a-méthyl 9a-fluoroprednisolone) chez des malades atteints d'arthrite rhumatismale**

**RÉSUMÉ**

On est en train d'étudier chez des sujets humains quatre nouveaux analogues de l'hydrocortisone, tous ayant un groupe méthyl en position 16a de la molécule stéroïde. Ces composés sont: 16a-méthyl 9a-fluoroprednisolone (dexaméthasone: Decadron), 16a-méthyl 9a-fluorohydrocortisone, 16a-méthylprednisolone et 16a-méthylhydrocortisone. Des essais biologiques sur des animaux ont montré que ces composés exercent, à de différents degrés, des effets physiologiques frappants, tels que l'action antiphlogistique augmentée sans dérangement correspondant du métabolisme électrolytique. On présente ici un résumé des observations préliminaires sur les effets de ces quatre composés nouveaux sur des malades atteints d'arthrite rhumatismale.

La détermination clinique du pouvoir antirhumatisme de ces composés par rapport à la prednisolone fut effectuée en comparant la quantité en milligrammes nécessaire pour maintenir un degré similaire d'amélioration des manifestations rhumatismales actives. Approximativement, le pouvoir antirhumatisme moyen de ces composés fut jugé comme il suit:

- 16a-méthyl 9a-fluoroprednisolone (dexaméthasone) environ sept fois plus forte que la prednisolone;
- 16a-méthyl 9a-fluorohydrocortisone environ trois fois plus forte;
- 16a-méthylprednisolone, environ un tiers plus forte;
- 16a-méthylhydrocortisone, environ 70% plus forte que la prednisolone.

L'efficacité thérapeutique de la dexaméthasone, un des nouveaux analogues méthylés, est maintenant en train d'être étudiée dans un grand groupe de malades atteints d'arthrite rhumatismale. Ce composé est le plus puissant de tous les stéroïdes antirhumatisme synthétisés jusqu'à présent et il supprime les manifestations de l'arthrite rhumatismale d'une manière très efficace en doses remarquablement petites. Un pouvoir antirhumatisme augmenté, cependant, n'indique pas, en soi même, de supériorité, et ces essais cliniques ne furent pas assez longs pour pouvoir juger si la dexaméthasone a des avantages thérapeutiques sur la prednisone ou la prednisolone chez des malades atteints

d'arthrite rhumatismale chez qui la thérapie stéroïde prolongée est indiquée.

**Observaciones clinicas sobre compuestos 16a-metil corticosteroides: ensayos terapéuticos preliminares de la dexametasona (16a-metil 9a-fluoroprednisolona) en enfermos con artritis reumatoide**

**SUMARIO**

Se estudian en sujetos humanos cuatro nuevos análogos de la hidrocortisona, teniendo todos un grupo metil en posición 16a de la molécula esteroide. Estos compuestos son: 16a-metil 9a-fluoroprednisolona (dexametasona: Decaron), 16a-metil 9a-fluorohidrocortisona, 16a-metilprednisolona y 16a-metilhidrocortisona. Ensayos biológicos sobre animales comprobaron que estos compuestos ejercen, a grados diferentes, efectos fisiológicos asombrosos, tales como una acción antiflogística aumentada sin desarreglo correspondiente del metabolismo electrolítico. Se presenta aquí un sumario de las observaciones preliminares sobre los efectos de estos cuatro compuestos nuevos sobre enfermos con artritis reumatoide.

La determinación clínica del poder antirreumático de estos compuestos en relación a la prednisolona se hizo, comparando el número de miligramos necesario para mantener un grado similar de mejoría de las manifestaciones reumáticas activas. Aproximadamente, el poder antirreumático medio de estos compuestos fué el siguiente:

- 16a-metil 9a-fluoroprednisolona (dexametasona)—unas siete veces más fuerte que la prednisolona;
- 16a-metil 9a-fluorohidrocortisona, unas tres veces más fuerte;
- 16a-metilprednisolona, cerca de una tercera más fuerte;
- 16a-metilhidrocortisona, un 70% más fuerte que la prednisolona.

La eficacia terapéutica de la dexametasona, uno de los nuevos análogos metilados, está en el curso de investigación en un gran grupo de enfermos con artritis reumatoide. Este compuesto es el más potente de todos los esteroides antirreumáticos sintetizados hasta ahora y tiene el poder de suprimir las manifestaciones de la artritis reumatoide de una manera muy eficaz en dosis destacadamente pequeñas. Un poder antirreumático aumentado no indica, sin embargo por sí, una superioridad; estos ensayos clínicos no fueron bastante extensos para poder decidir sobre las ventajas terapéuticas de la dexametasona sobre la prednisona o la prednisolona en enfermos con artritis reumatoide necesitando una terapia esteroide prolongada.

## ROSE-WAALER TEST USING A RAPIDLY PREPARED SERUM FRACTION

BY

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The use of a serologically active fraction of serum in parallel with whole serum, in testing for the sheep cell agglutinating factor in rheumatoid arthritis, was suggested by Svartz and Schlossmann (1953) and by Ziff, Brown, Badin, and McEwen (1954). Claims of higher sensitivity and specificity have been re-emphasized in more recent publications (Ziff, Brown, Lospalluto, Badin, and McEwen, 1956; Svartz and Schlossmann, 1957). Since 1956, sheep cell agglutination tests have been performed in this laboratory by Ziff's method, using absorbed serum, euglobulin fraction, and inhibition titres as criteria (Rose and Whillans, 1957). This experience confirms the view of Hess (1956) that, while the technique is laborious, it is not outside the scope of a laboratory doing routine serological tests.

Although the exact nature of the rheumatoid agglutinating factor is not yet elucidated, it is usually considered to migrate in an electrical field mainly with the gamma globulins (Lamont-Havers, 1955; Svartz and Schlossmann, 1955; Lospalluto and Ziff, 1956). Thulin (1955) considered it to be distributed over the faster moving gamma and beta globulins, while Heller, Kolodny, Lepow, Jacobson, Rivera, and Marks (1955) classified it mainly as a beta-lipoprotein. Recently Franklin, Kunkel, Müller-Eberhard, and Holman (1957) presented evidence from ultracentrifugal studies for a fast moving gamma globulin being responsible for the serological activity in rheumatoid arthritis and a similar view has been put forward by Svartz (1957).

The preparation of the euglobulin fraction used in Ziff's method is a time consuming process, so that a search was made for a simpler method of preparing the active fraction. In view of the above it appeared to us that a gamma globulin fraction would be desirable. Serum fractions consisting mainly of gamma globulins can be prepared, using ammonium sulphate for salting out, by prolonged standing. However, the rapid and simple method of

Wolfsohn, Cohn, Calvary, and Ichiba (1948) gives a complete precipitate in less than one hour, and when haemagglutination titres using this fraction and Ziff's euglobulin showed good parallelism it was decided to compare the two fractions further.

### Methods

#### Preparation of the Euglobulin Fraction (EU)

This was carried out according to the method of Ziff and others (1954). The precipitate was dissolved in physiological saline to give a 1 : 4 dilution compared with the original serum.

#### Preparation of the Ammonium Sulphate Fraction (AS)

9.6 ml. of a solution containing 193 g. ammonium sulphate and 40 g. sodium chloride per litre was pipetted into a 15-ml. centrifuge tube, and 0.4 ml. of the inactivated and absorbed serum layered on top. The two components were then mixed by slow, repeated inversion for about 2 minutes. The tube was now corked and centrifuged at 2,500-3,000 rpm in an M.S.E. Major centrifuge for 30 minutes, the supernatant poured off, and the tube allowed to stand in an inverted position on filter paper for a few minutes. The precipitate was then dissolved in 1.6 ml. physiological saline with the aid of a glass rod. This also gave a 1 : 4 dilution compared with the original serum and this was ready for use in the haemagglutination test.

#### Sensitized Sheep Cells

The sheep cells were collected in Alsever's solution containing 0.1 per cent. streptomycin sulphate and standardized to 0.5 per cent. working suspension, using an EEL nephelometer and a method similar to that previously described for complement-fixation tests (Whillans, 1950). The haemolysin was prepared according to the method of Sawyer and Bourke (1946) and its basic agglutinating titre (BAT) determined, using dilutions of haemolysin ranging from 1 : 100 to 1 : 2,000.

To 0.5 ml. of each dilution, 0.5 ml. of 0.5 per cent. sheep cell suspension was added. After the tubes had been kept overnight at 4° C., the cell pattern in the bottom of the tube was read by holding it over a concave mirror while illuminating it from the side with a lamp.

In high concentration of haemolysin, the cells form into a tightly patterned clump, often showing "chinese characters" in the centre. As the haemolysin concentration decreases, the cells fill the bottom of the tube, and as the concentration decreases still further, the cells form a pattern and then a button. The end point is shown by that tube containing a pattern which has in its next higher dilution a tube containing a button. This method of reading has proved much easier than that of Ziff and others (1956), and in our hands is more reproducible.

Using the information thus derived, cells were then sensitized by adding an equal amount of the appropriate dilution of haemolysin in 0.9 per cent. saline at 37° C. to 0.5 per cent. sheep cells in 0.9 per cent. saline also at 37° C., so that the final cell suspension contained either  $\frac{1}{4}$  or  $\frac{1}{2}$  BAT of haemolysin. After the mixed suspension had been kept at 37° C. for 30 minutes, the sensitized cells were ready for use.

#### Titration of Euglobulin (EU) and Ammonium Sulphate Fraction (AS)

Starting with a 1:4 dilution as prepared above, serial twofold dilutions of EU and AS fractions were prepared in 0.9 per cent. saline using 0.5 ml. volumes. To these were added 0.5 ml. of the appropriately sensitized cells. After standing overnight at 4° C., the cell pattern was read as above. The first tube represented a titre of 1:16 calculated as the final dilution.

#### Inhibition

This was carried out according to the method of Ziff and others (1954), but using both EU and AS fractions in twofold dilution series, the titre being read as above.

### Results

#### Comparisons between EU and AS Titres

Simultaneous haemagglutination tests were performed on EU and AS fractions prepared from a total of 280 sera. These had been sent to us for a routine performance of the Rose-Waaler test. Clinical diagnoses were not considered in this comparison. The diagnostic value of haemagglutination tests on serum fractions has been summarized by Ziff (1957).

Normal levels were established on the basis of haemagglutination tests on fractions derived from pooled donors' sera and on previous experience with fractions tested routinely.

(1) *Preliminary Series. Sensitizer 1:2 Basic Agglutinating Titre.*—In this series fifty fractions were compared. Of these, 31 sera had a raised titre and seventeen had a normal titre in both fractions. This gave an agreement of 96 per cent. In two cases (4 per cent.) the EU had a titre one tube above the normal level, while the corresponding AS was within normal limits.

(2) *Second Series. Sensitizer 1:4 Basic Agglutinating Titre.*—In this series, a reduction of haemolysin was tried, as it was thought desirable to keep the normal titre as low as possible. 94 fractions were compared, of which 58 showed a raised level and 32 a normal level in both fractions. In four cases (4.3 per cent.), the AS had a level of 1:32 (with the normal titre established at 1:16 or less) and the corresponding EU was within normal limits. Comparing titres, 45 fractions showed identical results, while 46 showed a one-tube difference and three a two-tube difference. We should, however, consider a one-tube difference to be within the experimental error of the method. This level of sensitization caused not only a slight drop in titre, but in three cases a reduction of sensitivity by shifting values from raised to normal range (e.g. Case 8, Table I).

(3) *Third Series. Sensitizer 1:2 Basic Agglutinating Titre.*—A further 136 sera were compared using 1:2 BAT. A normal titre of 1:32 or less was established using this level of sensitivity.

Of these sera, 88 showed raised titres and 43 normal titres in both fractions. In five cases (3.7 per cent.), one fraction showed a titre one tube above the normal limit while the other fraction was within the normal limit (four AS and one EU). Comparing titres, 62 fractions had identical titres, 64 showed a one-tube difference, and 10 (7.4 per cent.) showed a two-tube difference (Table I).

TABLE I  
EXAMPLES OF HAEMAGGLUTINATION TITRES ON FRACTIONS AND EFFECT OF CELL SENSITIZING DOSE

Sample	Basic Agglutinating Titre			
	1:2		1:4	
	Ammonium Sulphate	Euglobulin	Ammonium Sulphate	Euglobulin
1	16,384	32,768	4,096	4,096
2	2,048	2,048	2,048	1,024
3	1,024	1,024	512	256
4	1,024	512	256	128
5	256	128	256	128
6	128	128	64	64
7	128	64	128	64
8	64	64	16	16
9	32	16	16	Under 16
10	32	32	16	Under 16
Normal	32 or less		16 or less	

(4) *All Series considered Together.*—In a total of 280 comparisons between EU and AS titres, 96.1 per cent. showed agreement, being either normal or raised in both fractions. In 3.9 per cent., one fraction had a raised titre while the other was normal (eight AS, three EU). However, in each



of these cases the titre was only one tube above the level considered to be the upper limit of normal, and thus of little significance (Table II).

TABLE II  
COMPARISON OF HAEMAGGLUTINATION TESTS ON  
AMMONIUM SULPHATE AND EUGLOBULIN  
FRACTIONS IN 280 CASES

Result		No.	Per cent.
Agreement	Both AS and EU raised .. ..	177	
	Both AS and EU normal .. ..	92	
Total .. ..		269	96.1
Dis-agreement	EU normal, AS one tube above normal .. ..	8	2.8
	AS normal, EU one tube above normal .. ..	3	1.1
	One fraction normal, the other more than one tube above normal .. ..	0	0
	Total Cases .. ..	280	100

#### Importance of Preliminary Absorption with Sheep Cells

A comparison was made between titres using AS fractions before and after absorption with sheep cells, as the elimination of this step would simplify the procedure. In a small series of twenty fractions, four showed a two-tube difference and ten a one-tube difference, and six were identical. The negative control with unsensitized sheep cells showed definite agglutination in four fractions and doubtful agglutination in a further four. The positivity of the test was affected in three cases (15 per cent.) (Table III).

#### Inhibition Test

The inhibition test was performed simultaneously on the EU and AS fractions of 100 sera; 51 showed inhibition and 41 absence of inhibition in both fractions, while eight showed disagreement. Of the latter, five AS and three EU fractions showed absence of inhibition while inhibition was present in the corresponding fraction.

#### Discussion

The method of Wolfsohn and others (1948) for the estimation of gamma globulin has been adapted for the production of a serologically active fraction from the serum of cases of rheumatoid arthritis. This avoids a step involving 48 hours dialysis and is therefore more suited to routine use than is Ziff's euglobulin fraction. In comparison with the latter, it showed practically identical serological activity, the discrepancies being confined to a few cases in the doubtful range just above normal.

An electrophoretic analysis of fifteen sera and their corresponding ammonium sulphate fractions showed the AS fraction to consist mainly of gamma globulin with about 6-15 per cent. beta globulin, and to include almost the whole of the gamma globulin of the original serum. This finding is of the same order as that of Wolfsohn and others (1948).

The addition of sodium chloride to the ammonium sulphate solution as used above produces a complete precipitate of gamma globulin in less than an hour, compared with the long standing required when ammonium sulphate alone is used. The ease with which such a precipitate may be produced and used to estimate gamma globulins has been shown in previous viscometric studies (Fischman, 1957). It might be thought that the presence of residual salts would interfere with the haemagglutination reaction unless the precipitate was dialysed to reduce the ammonium sulphate and sodium chloride concentration, but results have shown this to be unnecessary. Further, comparative estimations of the agglutinating titre of haemolysin for sheep cells, using 0.9 per cent. saline without and with ammonium sulphate in the concentration found in the AS fraction diluted 1 : 8 as in the first tube of the test, showed no difference in agglutinating titre.

There is no agreement in the literature on the sensitizing dose of haemolysin. Thus, while Ziff and others (1954) used 1 : 2 BAT for their whole serum and euglobulin titres and 1 : 20 BAT for their inhibition tests, Scott (1952) and Gibson and Ling (1956) sensitized with 1 : 4 BAT, Heller,

TABLE III  
HAEMAGGLUTINATION TITRES BEFORE AND AFTER ABSORPTION WITH SHEEP CELLS  
IN TWENTY AMMONIUM SULPHATE FRACTIONS

Before Absorption				After Absorption			
Haemagglutination		Unsensitized Cell Control		Haemagglutination		Unsensitized Cell Control	
Raised	Normal	Positive	Doubtful	Raised	Normal	Positive	Doubtful
16	4	4	4	13	7	0	0



Jacobson, Kolodny, and Kammerer (1954) with 1:20 BAT, and Heller and others (1955) with 1:10 BAT. In our experience, 1:2 BAT has seemed preferable, but from batch to batch of haemolysin the appropriate amount has varied between 1:2 and 1:4 BAT, a BAT under 1:4 showing a considerable loss in sensitivity.

*Absorption with Sheep Cells.*—Craig, Kerby, and Persons (1957) suggested that, when a euglobulin fraction is used to test for haemagglutination, preliminary absorption with sheep cells may be omitted. No data were, however, presented to show whether these authors found an absence of heterophile antibodies in all samples, or whether they thought that the effect of their presence on the titre was negligible. In the small series tested in the present study, an appreciable effect on the titre was shown in 15 per cent. Preliminary absorption of the inactivated sera with sheep cells was therefore continued.

*Other Methods for preparing Serologically Active Fractions.*—While the cold precipitation method of Svartz and Schlossmann (1955) is somewhat simpler than the Ziff fractionation, it requires 48 hours chilling. Craig and others (1957) have recently described a rapid method for the production of a euglobulin fraction, using dilute hydrochloric acid. Although fast, it seems somewhat less convenient than the AS method, since it requires refrigeration and the use of a refrigerated centrifuge. In contrast, all steps in the ammonium sulphate precipitation can be carried out at room temperature within an hour.

Several methods have been proposed to replace the sheep cell haemolysin with FII globulin, in carrying out the titration either with sheep cells or with latex or other particles. Bartfeld, Mahood, and Hartung (1958), while emphasizing that with latex particles the procedure is simplified, test the serum only, as they consider the more sensitive fraction techniques unsuitable for routine diagnostic use because of their length and complexity. The present study suggests that, while the above remarks may apply to the inhibition technique and to agglutination techniques on fractions of Ziff and others or of Svartz and others, the AS fractionation is both simple and rapid, may be easily adapted for routine use, and would seem worthwhile for a trial in the FII technique.

*Inhibition.*—The AS fraction may also be used to perform the inhibition test as proposed by Ziff and others (1954) on the euglobulin fraction. These authors claimed higher specificity for the inhibition test than for the fraction haemagglutination titre,

but in general it was found impossible to reproduce this higher specificity, irrespective of the fraction used, and Ziff himself says that his test is difficult to adapt for routine use (Ziff, 1957). No attempt was made in the present study to evaluate the inhibition test as a routine practical procedure.

One technical difficulty seems to lie in the adjustment of the proper dilution of the known positive serum used. According to Ziff and others (1954), the positive serum is agglutinated with sheep cells sensitized with 1:20 BAT haemolysin, and one-eighth of this titre gives the dilution to be used in the inhibition titration. Using these criteria with one batch of positive serum, it was found that complete lack of inhibition occurred somewhat less frequently than a positive fraction titre in cases diagnosed as rheumatoid arthritis. A new batch of positive serum, however, which had the same titre as the previous one and was used in the same dilution, was not inhibited by any serum, including negative controls. A dilution five times greater than the previous one had to be used to obtain comparable results. This applied whether AS or EU fractions were used. This dilution gave higher sensitivity and specificity than was obtained by using the previous serum, and gave a better correlation with the fraction haemagglutination titre. Any attempt to increase the sensitivity, however, resulted in absence of inhibition in normal control sera. It seems that one has to decide on the level to be used in an arbitrary fashion. We attempted to keep our normal level at 1:32.

### Summary

A simple method of producing a gamma globulin fraction of whole serum for use in the Rose-Waaler test is described. It is produced in less than an hour at room temperature, and is suitable for demonstrating both the haemagglutination and inhibition factors.

A comparison between 280 simultaneous haemagglutination tests on this fraction and the euglobulin fraction described by Ziff and associates gave similar raised or normal results in 96.1 per cent. of cases. In the remainder, the euglobulin fraction was normal with the ammonium sulphate fraction one doubling dilution above normal in 2.8 per cent., of cases, and the ammonium sulphate fraction was normal with the euglobulin fraction one doubling dilution above normal in 1.1 per cent. of cases.

Inhibition titres performed on both fractions according to the method of Ziff and his associates gave identical results in 92 per cent. of cases.

Some problems relating to the level of sensitization

of sheep cells with haemolysin and the use of a routine inhibition test are discussed.

This ammonium sulphate precipitated fraction offers a rapid and convenient alternative to lengthy methods requiring either dialysis or cold precipitation for the preparation of material for the Rose-Waaler test.

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# Réaction de Rose-Waaler à l'aide d'une fraction sérique rapidement préparée

## RÉSUMÉ

On décrit un simple procédé pour préparer la fraction globuline gamma du sérum complet pour la réaction de Rose-Waaler. On la produit en moins d'une heure à la température ambiante et elle se prête à décélérer aussi bien les facteurs hémagglutinants que les inhibiteurs.

En comparant 280 réactions d'hémagglutination simultanées à l'aide de cette fraction et à l'aide de la fraction d'euglobine selon Ziff et col., on obtint les mêmes résultats, élevés ou normaux, dans 91,1% des cas. Dans le reste, la réaction à l'aide de la fraction

d'euglobine fut normale tandis que la réaction à l'aide de la fraction précipité par le sulfate d'ammonium fut une dilution double au dessus de la normale dans 2,8% des cas; l'inverse eut lieu dans 1,1% des cas.

Les réactions d'inhibition avec les deux fractions, selon la méthode de Ziff et col., donnèrent des résultats identiques dans 92% des cas.

On discute quelques problèmes concernant le degré de sensibilisation des globules de mouton avec de l'hémolysine et l'emploi régulier de la réaction d'inhibition.

La fraction précipité par le sulfate d'ammonium offre une alternative commode à des procédés laborieux demandant soit une dialyse, soit une précipitation au froid, pour préparer du matériel pour la réaction de Rose-Waaler.

# Reacción de Rose-Waaler empleando una fracción sérica rápidamente preparada

## SUMARIO

Se describe un simple método de preparar la fracción globulina gama del suero completo para la reacción de Rose-Waaler. Esta fracción se obtiene en menos de una hora en la temperatura ambiente y se puede emplear para evidenciar tanto los factores hemagglutinantes como inhibidores.

Al comparar 280 reacciones de hemagglutinación simultáneas con esta fracción y con la fracción de euglobina, según el modo de Ziff y col., se obtuvieron cifras parecidas, altas o normales, en un 91% de los casos. En los demás, la reacción con la fracción de euglobina fué normal mientras que la reacción con la fracción precipitada por el sulfato de amonio fué una doble dilución por encima de lo normal en un 2,8% de los casos; el resultado fué inverso en un 1,1% de los casos.

La reacción de inhibición con ambas fracciones, según el método de Ziff y col., dió resultados idénticos en un 92% de los casos.

Se discuten ciertos problemas respecto al grado de sensibilización de los glóbulos de oveja con hemolisina y el empleo regular de la reacción de inhibición.

La fracción precipitada por el sulfato de amonio ofrece una alternativa útil a los procedimientos fastidiosos que exigen sea una dialisis sea precipitación por el frío en la preparación del material para la reacción de Rose-Waaler.

## OSTEO-ARTHROSIS AND DISK DEGENERATION IN AN URBAN POPULATION\*

BY

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This study of osteo-arthritis, or degenerative joint disease, is based on the same survey material as the corresponding paper on rheumatoid arthritis (Kellgren and Lawrence, 1956). A one-in-ten random sample of the population aged 55-64 years in the Lancashire town of Leigh was studied clinically, radiologically, and serologically for all forms of arthritis. After a detailed clinical examination of the joints, routine *x* rays were taken of the hands, feet, pelvis, knees, and cervical and lumbar spine, and a blood sample was taken for the sheep cell agglutination test (SCAT). The clinical and radiological part of the survey was 79 per cent. complete. In a previous survey of rheumatic complaints made in the town of Leigh in 1949-50, osteo-arthritis was diagnosed on clinical grounds more frequently than any other form of rheumatism (Kellgren, Lawrence, and Aitken-Swan, 1953). The prevalence of complaints attributable to osteo-arthritis was exceptionally high in females over 50 years of age, and in this sex was more often polyarticular and was less closely associated with trauma or occupation than in males. A separate study of patients seen at the University Rheumatism Clinic had shown that women frequently suffer from a polyarticular form of osteo-arthritis which has a distinct symptomatology, course, and pattern of joint involvement. This condition has been described as "primary generalized osteo-arthritis" (Kellgren and Moore, 1952). The present study was designed to obtain more precise information about this condition, and to investigate causative factors in osteo-arthritis in general.

For details of sampling and for the method of conducting the survey, the paper on rheumatoid arthritis should be consulted. At the clinical examination all persons seen were given a grading for rheumatoid arthritis and for local and generalized osteo-arthritis. The *x* rays were later read by two observers in consultation. Problems of observer

error and observer difference in reading *x* rays for rheumatic disorders have been discussed in previous papers (Kellgren and Lawrence, 1952; Lawrence, 1955; Kellgren and Bier, 1956). The particular problems of observer difference in relation to osteo-arthritis and the standard gradings used for radiological osteo-arthritis in this study have been described elsewhere (Kellgren and Lawrence, 1957).

In reading *x* rays of the spine, the classification of Collins (1949) has been followed; the term osteo-arthritis is confined to disease in the apophyseal joints, whereas osteophytosis of vertebral bodies and narrowing of disk spaces are referred to as disk degeneration.

In determining the number of joints affected by osteo-arthritis each type of joint was considered as a group. Thus the distal interphalangeal joints of the fingers of both hands were considered as one group, the knees as another, and the apophyseal joints of the cervical spine as a third. In each group, osteo-arthritis was divided into five grades of severity (0 to 4) as in previous papers, the worst joint in the group being used to assess the grading.

### Results

#### Prevalence of Osteo-Arthritis and Disk Degeneration

In the 55-64 age group, some radiological evidence of osteo-arthritis was almost universal (Table I, opposite).

Of those who attended for *x* ray, 83 per cent. of males and 87 per cent. of females had radiological evidence of osteo-arthritis in one or other of the joints *x* rayed. The actual prevalence in the population, however, may have been slightly lower than this since there were fewer persons with rheumatic pain amongst the refusals than in those attending for *x* ray. The proportions are, therefore, assessed both from the total population sample and from the total of those attending for *x* ray, thus giving a "minimal" and "maximal" prevalence. The true proportion should fall between these values.

\* The material for this study was collected in 1954 with the aid of a grant from the Medical Research Council.



TABLE I  
PREVALENCE OF RADIOLOGICAL OSTEO-ARTHROSIS AND DISK DEGENERATION IN A  
RANDOM SAMPLE OF 204 MALES AND 277 FEMALES AGED 55-64

Type of Affection		Males				Females				Maximal Prevalence
		Total No. X-rayed	Grades 2-4			Total No. X-rayed	Grades 2-4			Significance of Difference between Sexes ( <i>P</i> )
			No.	in per cent. of Total			No.	in per cent. of Total		
				X-rayed: Maximal	Sample: Minimal			X-rayed: Maximal	Sample: Minimal	
Osteo-arthritis	Total .. .. .	173	143	83	70	207	183	88	66	<0.12
	More than three Joint Groups .. .. .	173	51	29	25	207	97	47	35	<0.001
	With Symptoms .. .. .	173	73	42	35	207	121	58	44	<0.003
Disk Degeneration .. .. .		170	141	83	69	201	145	72	52	<0.02

N.B.—As set out in this Table, maximal prevalences have been calculated as a percentage of the total attending for x ray, and minimal prevalences as a percentage of the total in the sample. Significances in this paper are assessed from  $\chi^2$ , using either the  $2 \times 2$  table, with correction for continuity where required, or Yates' comparison of mean scores.

Only if the refusals had more osteo-arthritis than the respondents would the true prevalence be greater than "maximum" as here stated.

The proportion of individuals with some osteo-arthritis was not markedly greater in females than in males, but osteo-arthritis in multiple joints was more frequent in females. Disk degeneration on the other hand was more frequent in males.

With a view to elucidating the factors responsible for this sex difference, the pattern of joint involvement was studied.

#### Pattern of Joint Involvement

The proportion of each group of joints affected by osteo-arthritis is illustrated in Fig. 1 (see also Table II, overleaf). Some joints are almost universally affected whereas others are almost completely spared.

In males cervical and lumbar disk degeneration completely overshadowed osteo-arthritis even of joints so commonly affected as the distal interphalangeals, but in females disk degeneration had a similar frequency to osteo-arthritis of the fingers.

A certain pattern of joint involvement was common to both sexes, but there were also sex differences. Thus the distal interphalangeal joints of the fingers and first metatarsophalangeal joints of the feet were most commonly affected in both sexes, but beyond this the pattern was quite different. The females had far more osteo-arthritis in the distal and proximal interphalangeal joints of the fingers, in the first carpometacarpal joints, and in the metatarsophalangeal joints. The males had more involvement of the wrists and hips. Certain other differences were suggestive, notably the increased affection of the knees and sacro-iliac joints in females.

When only those with moderate or severe grades are

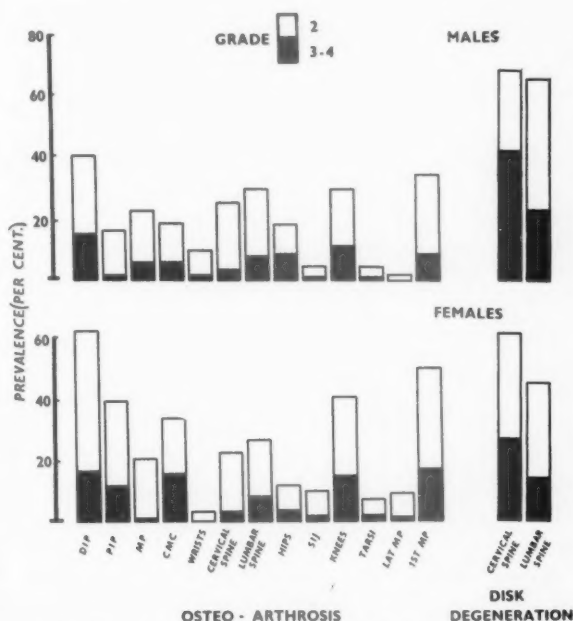


Fig. 1.—Pattern of osteo-arthritis and disk degeneration in males and females.

Each column represents the proportion of groups of joints x rayed which showed radiological signs of osteo-arthritis or disk degeneration. The grade recorded is that of the most severely affected joint in each group.

considered, disk degeneration was still more prevalent in males, but the sex difference for osteo-arthritis was in general less marked. Females, however, still had more disease in the distal and proximal interphalangeal and first carpometacarpal joints of the hands, in the knees, and in the metatarsophalangeal joints of the feet, and the males more in the metacarpophalangeal joints, wrists, and hips.



TABLE II  
JOINT PATTERN OF RADIOLOGICAL OSTEO-ARTHRITIS AND DISK DEGENERATION

Joints Affected		Males			Females		
		Total x-rayed	Grade		Total x-rayed	Grade	
			2-4	3-4		2-4	3-4
Osteo-arthritis	D.I.P. } Hands	173	71	19	206	128	35
	P.I.P. } ..	173	30	4	206	82	25
	M.P. } ..	173	40	11	206	42	3
	First C.M.C. } ..	173	33	11	206	69	33
	Wrists ..	172	17	3	205	9	0
	Cervical Spine ..	170	45	6	201	45	6
	Lumbar Spine ..	165	49	13	193	53	14
	Hips ..	167	31	14	191	23	6
	Sacro-iliac Joints ..	164	9	2	191	20	3
	Knees ..	171	51	19	199	81	30
	Tarsi ..	173	9	2	206	15	6
	Lateral M.P. } Feet	173	4	0	206	18	2
	First M.P. } ..	173	61	15	206	104	36
	Total ..	173	143	75	207	183	97
Disk Degeneration	Cervical Spine ..	170	116	70	201	124	55
	Lumbar Spine ..	165	109	38	193	86	25

N.B.—The shoulders, elbows and ankles were not routinely x rayed. No assessment of the prevalence of osteo-arthritis in these joints is therefore possible.

It would thus appear likely, on the grounds both of total prevalence and of pattern of joint involvement, that the factors producing osteo-arthritis are not identical in the two sexes. With a view to elucidating this further, the effect of known causative factors, such as injury, occupation, and body weight, were considered in relation to sex and joint pattern.

**Injury.**—In a proportion of those with osteo-arthritis, there was either a history of previous trauma or radiological evidence of an injury. The prevalence of traumatic osteo-arthritis so defined in males and females is compared in Fig. 2 and Table III.

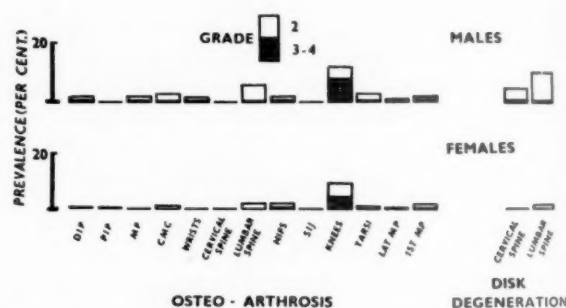


Fig. 2.—Pattern of osteo-arthritis and disk degeneration recorded as being related to injury in males and females.

TABLE III  
INJURY IN RELATION TO RADIOLOGICAL OSTEO-ARTHRITIS AND DISK DEGENERATION

Joints Affected		Males			Females		
		Total x-rayed	Related to Injury Only		Total x-rayed	Related to Injury Only	
			Grade 2-4	Grade 3-4		Grade 2-4	Grade 3-4
Osteo-arthritis	D.I.P. } Hands	173	4	2	206	1	1
	P.I.P. } ..	173	1	1	206	1	1
	M.P. } ..	173	3	2	206	0	0
	C.M.C. } ..	173	5	1	206	2	1
	Wrists ..	172	2	1	205	0	0
	Cervical Spine ..	170	0	0	201	0	0
	Lumbar Spine ..	165	11	1	193	3	0
	Hips ..	167	4	2	191	3	1
	Sacro-iliac Joints ..	165	0	0	191	0	0
	Knees ..	171	21	13	199	18	8
	Tarsi ..	173	5	1	206	1	0
	Lateral M.P. } Feet	173	1	0	206	1	1
	First M.P. } ..	173	3	2	206	2	1
	Total ..	173	60	26	207	31	14
Disk Degeneration	Cervical Spine ..	170	8	3	201	0	0
	Lumbar Spine ..	165	16	2	193	2	1

Our previous study had shown that a history of injury was more frequently encountered in males. In the present study, 35 per cent. of the males and 15 per cent. of the females were found to have osteo-arthritis at the site of an injury. In both sexes the knees most frequently showed this association and indeed few females had traumatic osteo-arthritis at any other site. In males, the lumbar spine was frequently involved, and though disk degeneration was more commonly associated with back injury, osteo-arthritis was also often found in those with such a history, usually in conjunction with disk degeneration. Less frequent sites of post-traumatic osteo-arthritis in males were the first carpometacarpal joints and the tarsi. The shoulders and elbows were not x rayed as a routine in this study, but symptoms and signs of osteo-arthritis were not uncommonly encountered in association with a history of injury in both these joints.

A comparison of the joint pattern of post-traumatic osteo-arthritis with the general pattern makes it clear that trauma produces a distinctive pattern and is an important factor in males. Indeed, in men, trauma was associated with osteo-arthritis in about half of the affected knees and tarsal joints, and in a proportion of certain other joints, such as the lumbar spine, hips, wrists, and first carpometacarpals, and this association was most prominent when the osteo-arthritis was of moderate or severe degree. Injury, however, appeared to have a negligible influence on the general pattern of osteo-arthritis in females, and did not explain the more frequent multiple joint involvement in this sex.

**Occupation.**—The data in Table IV refer to predominant occupation and not necessarily to employment at the time of the survey.

In this sample of males, both the 74 miners and the eighteen cotton workers had more osteo-arthritis than the 81 men engaged in other miscellaneous occupations, but the joints affected were different in these two occupational groups.

In the miners the lumbar spine and knees were significantly more affected ( $P < 0.01$ ) and the hips and metacarpophalangeal joints showed a suggestive trend. The most striking feature in the miners, however, was the excess of lumbar disk degeneration ( $P < 0.003$ ). These findings are in agreement with our previous results (Kellgren and Lawrence, 1952). In the cotton workers all the small joints of the hands and the cervical spine appeared to be more frequently affected, but the number of cotton workers was too small for the observed differences to reach accepted levels of significance except in the first carpometacarpal joints ( $P < 0.01$ ).

The miscellaneous group was made up of small numbers of men engaged in a wide variety of occupations which could not usefully be analysed.

In the females of this age group, domestic work overshadowed all other types of work and was the predominant occupation in 130 (63 per cent.). Even in those whose occupation had been predominantly non-domestic, household chores probably occupied a large part of their time. It is therefore not surprising that the pattern of osteo-arthritis in housewives was almost identical with the pattern found in all females and that no significant differences were

TABLE IV

PREDOMINANT OCCUPATION IN RELATION TO RADIOLOGICAL OSTEO-ARTHRITIS AND DISK DEGENERATION

Joints Affected		Males									Females								
		Miners			Cotton Workers			Others			Domestic			Cotton Workers			Others		
		No. x-rayed		Grade 2-4		No. x-rayed		Grade 2-4		No. x-rayed		Grade 2-4		No. x-rayed		Grade 2-4		No. x-rayed	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Osteo-arthritis	D.I.P. } Hands	74	33	45	18	10	56	81	28	35	130	80	62	50	32	64	26	16	62
	P.I.P. }	74	14	19	18	6	33	81	10	25	130	49	38	50	24	48	26	9	35
	M.P. }	74	20	27	18	6	33	81	14	17	130	26	20	50	9	18	26	7	27
	C.M.C. }	74	13	18	18	8	44	81	12	15	130	41	52	50	20	40	26	8	31
	Wrists	73	8	11	18	2	11	81	7	9	129	5	4	50	3	6	26	1	4
	Cervical Spine	74	19	26	17	7	41	79	19	24	128	24	19	48	12	25	25	9	36
	Lumbar Spine	71	29	41	17	4	24	77	16	21	124	33	27	45	15	33	24	5	21
	Hips	73	15	21	17	3	18	77	13	17	122	13	11	45	4	9	24	6	25
	Sacro-iliac Joints	72	4	6	17	1	6	75	4	5	122	12	10	45	6	13	24	2	8
	Knees	74	31	42	17	4	24	80	16	20	127	56	44	47	15	32	25	10	40
	Tarsi	74	1	1	18	1	6	81	7	9	129	9	7	50	4	8	27	2	7
	Lateral																		
	M.P. } Feet	74	2	3	18	1	6	81	1	1	129	12	9	50	4	8	27	2	7
	First M.P. }	74	26	35	18	7	39	81	28	35	129	61	47	50	29	58	27	14	52
	Total	74	65	88	18	17	95	81	60	74	130	114	88	50	45	90	27	24	89
Disk Degeneration	Cervical Spine	74	51	70	17	14	83	79	51	65	128	78	61	48	30	62	25	16	64
	Lumbar Spine	71	56	79	17	11	65	77	42	55	123	58	47	46	17	37	24	11	46

found between the housewives and the women who were working outside the home.

**Obesity.**—An association between osteo-arthritis and obesity was indicated by the findings of Fletcher and Lewis-Faning (1945). In the present study obesity was assessed from standard height/weight tables (Abrahams and Widdowson, 1940), those more than 10 per cent. above average weight being classified as obese. On this basis, 27 per cent. of

the males and 44 per cent. of the females were considered to be overweight. The pattern of osteo-arthritis in obese individuals (Fig. 3 and Table V) differed in several respects from that in the remainder of the population. In both sexes the metatarsophalangeal joint of the great toe was more commonly affected by osteo-arthritis in the obese ( $P < 0.004$  in males,  $< 0.01$  in females). The knee joint was affected more than twice as often in obese females

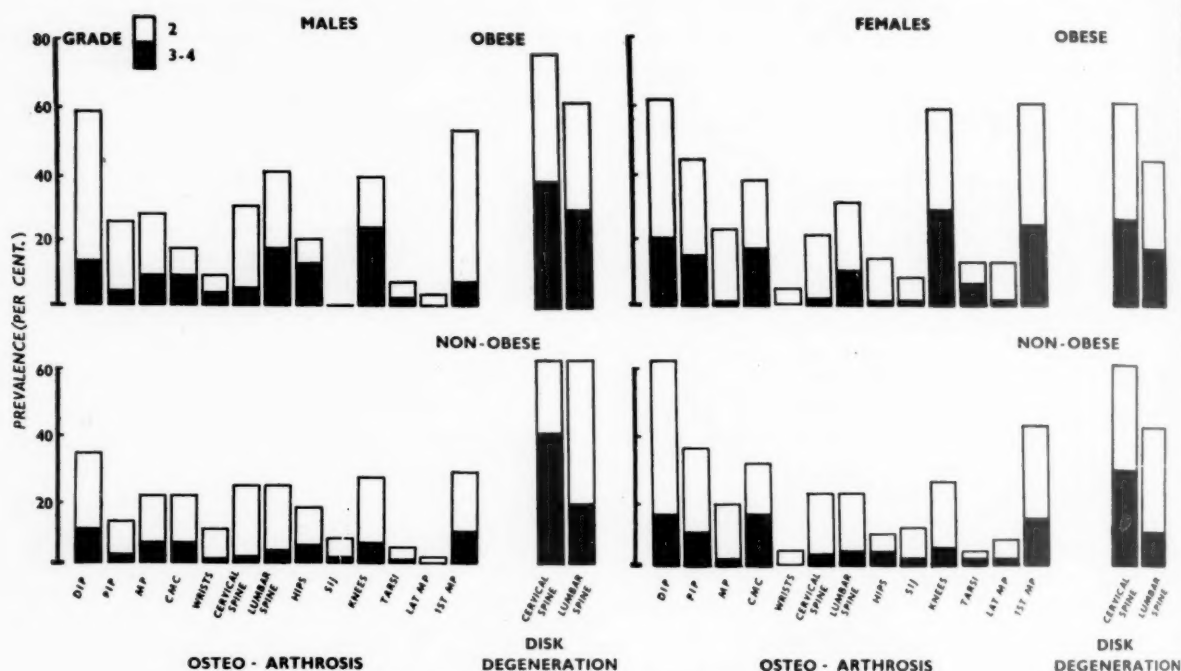


Fig. 3.—Pattern of osteo-arthritis and disk degeneration in obese and non-obese males and females.

TABLE V  
OBESITY IN RELATION TO RADIOLOGICAL OSTEO-ARTHRITIS AND DISK DEGENERATION

Joints Affected		Males						Females					
		Obese			Non-Obese			Obese			Non-Obese		
		No. x rayed	Grade		No. x rayed	Grade		No. x rayed	Grade		No. x rayed	Grade	
			2-4	3-4		2-4	3-4		2-4	3-4		2-4	3-4
Osteo-arthritis	D.I.P. } Hands	46	27	6	127	44	13	86	54	17	120	74	18
	P.I.P. }	46	12	2	127	18	2	86	38	13	120	44	12
	M.P. }	46	13	4	127	27	7	86	20	1	120	22	2
	C.M.C. }	46	8	4	127	25	7	86	33	15	120	36	18
	Wrists	45	4	2	127	13	1	85	4	0	120	5	0
	Cervical Spine	46	14	3	124	31	3	85	19	2	116	26	4
	Lumbar Spine	45	19	8	120	30	5	81	27	8	112	26	5
	Hips	46	9	6	121	22	8	80	12	1	111	11	5
	Sacro-iliac Joints	45	0	0	119	9	2	81	7	1	110	13	2
	Knees	46	18	11	125	33	8	84	51	24	115	30	6
	Tarsi	46	3	1	127	6	1	86	11	5	120	4	1
	Lateral M.P. } Feet	46	2	0	127	2	0	86	10	1	120	8	1
	First M.P. }	46	25	3	127	36	12	86	53	21	120	51	15
Total		46	40	26	127	102	35	87	80	48	120	101	49
Disk Degeneration	Cervical Spine	46	36	18	124	80	52	85	53	22	116	71	33
	Lumbar Spine	45	29	14	120	79	24	81	38	14	112	48	11

$P < 0.000,01$ ) and was also more often affected in obese males, the difference being greatest in severe grades of change ( $P < 0.004$ ). The lumbar spine was also more commonly affected by osteoarthrosis in males ( $P < 0.05$ ). A surprising finding was that, in obese males, the distal interphalangeal joints of the fingers were more affected ( $P < 0.01$ ). This did not apply to obese females, but the joint pattern in obese males resembled that in the total females.

#### Rheumatoid Arthritis

This is frequently mentioned as a causative factor in osteoarthrosis. In this series clinical rheumatoid arthritis or past polyarthritis was associated with an increased prevalence of osteoarthrosis in some joints, for example the carpometacarpal joints, wrists, and lumbar spine in males, and the knees in females; there was less in other joints and none of the differences were significant statistically. Nor was the number of joints affected by osteoarthrosis in females greater in those with either clinical or radiological evidence of rheumatoid arthritis or a positive sheep cell test. There was, however, in males a trend towards osteoarthrosis of multiple joints in those with clinical or radiological evidence of rheumatoid arthritis, but no clear relationship between the results of the sheep cell test and osteoarthrosis. It may be concluded, therefore, that rheumatoid arthritis does not affect appreciably the general pattern of osteoarthrosis in females of this age group, but may do so to some extent in males.

#### Paget's Disease

Radiological evidence of this condition in the parts x rayed in this series was encountered in thirteen males and two females. The prevalence was thus 8 per cent. in males and 1 per cent. in females. All those with Paget's disease had osteoarthrosis. It may be concluded, therefore, that rheumatoid arthritis does not affect appreciably the general pattern of osteoarthrosis in females of this age group, but may do so to some extent in males.

#### Mechanical Factors

Congenital deformities were rarely encountered in this series. Congenital dislocation of the hip, sacralization of the 5th lumbar vertebra, and short 4th and 5th metacarpals were each encountered once, and spondylolisthesis was seen eleven times (in eight females and three males). Of those with spondylo-

listhesis, eight had osteoarthrosis of the lumbar spine; more than in the general population sample.

Hallux valgus was encountered in greater or less degree in most of the sample. Only the more severe degrees were related to osteoarthrosis of the first metatarsophalangeal joint.

It may be concluded that deformities of sufficient grade to predispose to osteoarthrosis are too infrequent to affect the general pattern of the disease.

#### Constitutional Factor

Stecher (1955) has produced evidence that the digital nodes described by Heberden (1802) are inherited as a single autosomal gene, dominant in females and possibly recessive in males. An association between Heberden's nodes and osteoarthrosis of multiple joints has long been recognized, having been observed by Haygarth (1805). As this condition is commoner in middle-aged women it was labelled "menopausal" by Cecil and Archer (1926), but Kellgren and Moore (1952) found no accurate correlation with the menopause. Stecher found no evidence of an association between Heberden's nodes and osteoarthrosis elsewhere, but his investigation was based on a clinical examination.

Table VI, and Fig. 4 (overleaf), suggest a definite association between clinical Heberden's nodes and radiological evidence of multiple osteoarthrosis in both sexes, though this is most marked in the females. If we compare the distribution of radiological signs of osteoarthrosis in multiple joints in individuals with definite clinical nodes and in those who have no nodes or only doubtful clinical changes, the association between Heberden's nodes and radiological signs of multiple osteoarthrosis is highly significant ( $P < 0.003$  in males and  $< 0.00000001$  in females).

TABLE VI  
CLINICAL HEBERDEN'S NODES AND JOINT GROUPS  
SHOWING RADIOLOGICAL OSTEO-ARTHRISIS

No. of Joint Groups showing Radiological Osteoarthrosis	Males			Females		
	X-rayed	Heberden's Nodes		X-rayed	Heberden's Nodes	
		Absent	Present		Absent	Present
0-2	99	90	9	79	71	8
3-5	52	40	12	97	60	37
6+	22	7	15	31	8	23
Total	173	137	36	207	139	68

The reason for the discrepancy between our own results and those of Stecher is probably due to our different approach to the problem. Whereas



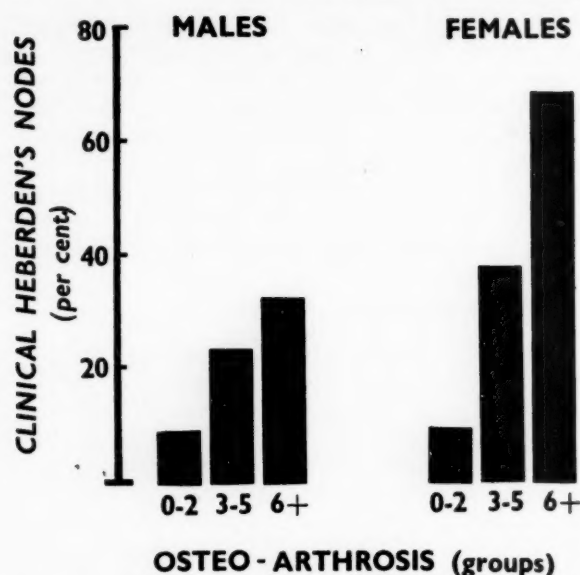


Fig. 4.—Relationship between definite Heberden's nodes, as recorded at the clinical examination, and the number of groups of joints showing definite radiological signs of osteo-arthritis in males and females.

Stecher used a clinical approach, we have assessed osteo-arthritis radiologically. Since the anatomical changes of osteo-arthritis are only occasionally associated with appropriate symptoms, the majority of these changes would remain unrecognized in the type of clinical study conducted by Stecher. The radiological method used by us, on the other hand, readily demonstrates all except the earliest anatomical changes of osteo-arthritis.

The pattern of joint involvement in males and females with and without radiological signs of osteo-arthritis of the distal interphalangeal joints of the fingers is shown in Table VII and Fig. 5 (opposite).

The individuals with osteo-arthritis of the distal interphalangeal joints clearly also have much more osteo-arthritis of all the other joints, this association being specially pronounced in females. In both sexes this association is most marked in the small joints of the hands and feet, the interfacetal joints of the cervical and lumbar spine, and the knees. This corresponds well with the picture of generalized osteo-arthritis described previously (Kellgren and Moore, 1952).

In males disk degeneration shows no such association with osteo-arthritis of the distal interphalangeal joints, but females with osteo-arthritis of the distal interphalangeal joints do have some excess of disk degeneration in the lumbar spine and also of osteo-arthritis in the sacro-iliac joints.

### Discussion

The main findings which emerge from this study are that osteo-arthritis when present usually affects many joints and has a rather characteristic pattern of joint involvement. The pattern of joint involvement, the severity of the changes in the individual joints, and the number of joints affected, are all more pronounced in females than in males. These findings suggest that a major factor in the causation of osteo-arthritis may be some sex-linked metabolic characteristic.

A high prevalence of osteo-arthritis in the distal interphalangeal joints in females has long been recognized in the form of Heberden's nodes, and a clear association between these nodes and radiological signs of osteo-arthritis in multiple joints has been demonstrated in both sexes but especially in females.

Stecher (1955) has suggested that the factor responsible for Heberden's nodes is inherited as a single autosomal gene dominant in females and possibly recessive in males. This factor need not be specific for Heberden's nodes in particular, but may be a tendency to osteo-arthritis in general, which expresses itself more strongly in the fingers of females because of the special mechanical stresses to which their fingers are exposed in domestic work.

In males, the basic pattern of osteo-arthritis is modified to a great extent by occupational stresses and also by individual episodes of trauma, so that in this sex environmental mechanical factors play an important part in determining both the severity and the site of osteo-arthritis.

The effect of obesity is apparent in both sexes and is mainly associated with an excess of osteo-arthritis in the weight-bearing joints suggesting a mechanical effect, but in males obesity is also associated with an excess of osteo-arthritis of the distal interphalangeal joints and the general pattern of osteo-arthritis in obese males approximates to that seen in the total females. This is not due to occupational stresses since the occupational spectrum of the obese males did not differ from that of the total males.

A hereditary tendency to osteo-arthritis has been encountered in animals other than man, for example, in certain inbred strains of mice. It closely simulates its human counterpart in anatomical features, in its relationship to postural characteristics, and in its occurrence in older age groups (Sokoloff, 1956). It may be modified by external factors, such as a high fat diet in susceptible strains, though it is little affected by such diet in other strains. To some extent this may be related in mice to strain differences in thyroid activity, but even in the absence

TABLE VII

RADIOLOGICAL HEBERDEN'S NODES IN RELATION TO JOINT PATTERN OF RADIOLOGICAL OSTEO-ARTHROSIS AND DISK DEGENERATION

Joints Affected		Males						Females						
		Radiological Heberden's Nodes (Osteo-Arthrosis D.I.P.)												
		Absent (Grade 0-1)			Present (Grade 2-4)			Absent (Grade 0-1)			Present (Grade 2-4)			
		Radiological Osteo-Arthrosis and Disk Degeneration in Other Joint Groups												
		Total x rayed	Grade		Total x rayed	Grade		Total x rayed	Grade		Total x rayed	Grade		
		2-4	3-4		2-4	3-4		2-4	3-4		2-4	3-4		
Osteo-arthritis	D.I.P.	Hands	102	0	0	71	71	19	0	0	0	128	128	35
	P.I.P.		102	3	1	71	27	3	78	10	1	128	72	24
	M.P.		102	12	1	71	28	10	78	5	0	128	37	3
	C.M.C.		102	9	0	71	24	11	78	8	4	128	61	29
	Wrists	101	6	1	71	11	2	78	1	0	127	8	0	
	Cervical Spine	99	18	0	71	27	6	75	6	0	125	39	6	
	Lumbar Spine	95	18	3	70	31	10	71	14	2	121	39	12	
	Hips	96	15	6	71	16	8	73	7	3	118	16	3	
	Sacro-iliac Joints	94	4	1	70	5	1	72	3	0	119	17	3	
	Knees	100	17	4	71	34	15	76	24	8	123	57	22	
	Tarsi	102	4	0	71	5	2	77	2	0	128	13	6	
	Lateral M.P.	102	1	0	71	3	0	77	5	1	128	13	1	
	First M.P.	102	25	5	71	36	10	77	21	9	128	82	27	
	Total		102	71	22	71	69	24	78	54	23	128	121	39
Disk Degeneration	Cervical Spine	99	62	39	71	54	31	75	43	13	125	81	42	
	Lumbar Spine	95	58	17	70	51	21	71	19	5	121	67	20	

N.B.—In counting the total with osteo-arthrosis, the D.I.P. joints have been excluded.

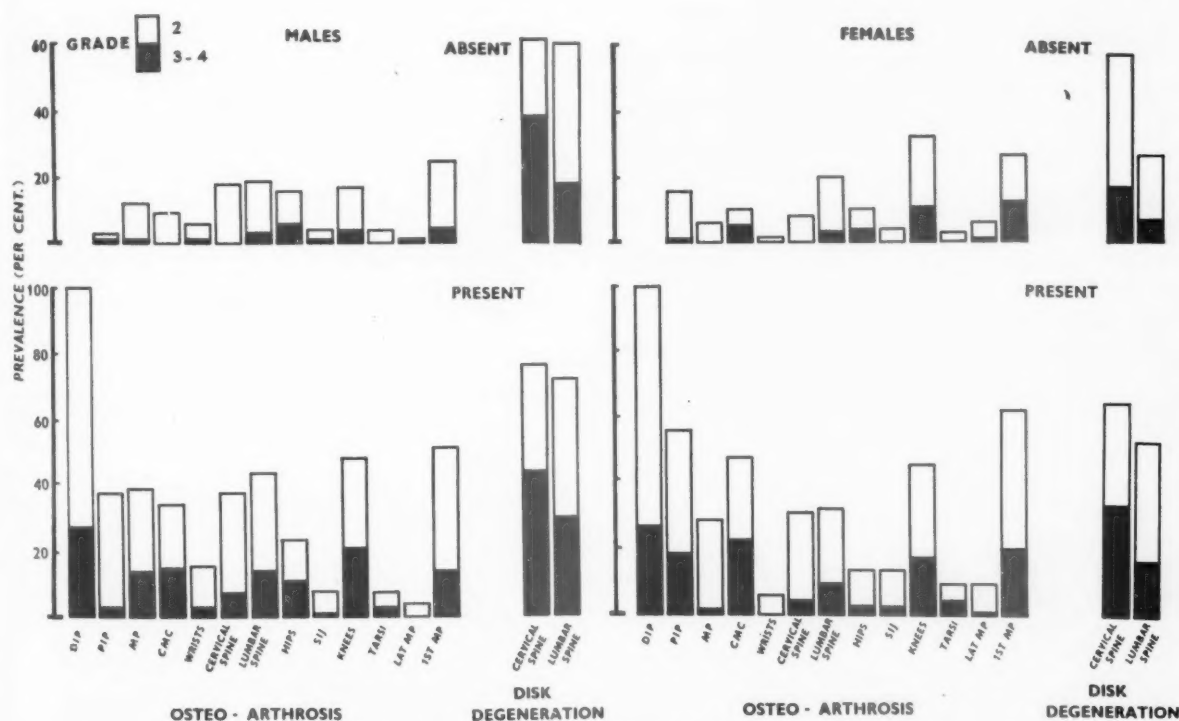


Fig. 5.—Pattern of osteo-arthrosis and disk degeneration in males and females in whom definite radiological signs of osteo-arthrosis of the distal interphalangeal joints were absent or present.

of thyroid secretion following radiothyroidectomy strain differences in susceptibility to osteo-arthritis on a high fat diet are found (Silberberg and Silberberg, 1955). It is unrelated to skeletal ageing as determined by epiphyseal union, though the degree of fusion of epiphyses is also determined genetically (Sokoloff and Jay, 1956).

Disk degeneration does not appear to be associated with generalized osteo-arthritis, and we have as yet no evidence about constitutional factors causing this condition except in certain rare diseases like alkaptonuria, but degeneration of the lumbar disks is very closely related to the mechanical stresses inherent in certain laborious occupations such as coal mining and also to individual episodes of trauma.

### Summary

The prevalence of degenerative joint disease in a population sample of 380 persons between the ages of 55 and 64 years has been investigated clinically and radiologically.

Previous indications of a relatively greater prevalence of intervertebral disk degeneration in males and of osteo-arthritis in females have been confirmed. It has been demonstrated that in females osteo-arthritis more often affects multiple joints. Factors responsible for these sex differences have been investigated.

The higher prevalence of osteo-arthritis in females was unrelated to occupation, to a history of injury, or to evidence of rheumatoid arthritis. Obesity was more frequent in females and was associated with an increased prevalence of osteo-arthritis of the weight-bearing joints, but did not account for the high prevalence of multiple osteo-arthritis in females. Heberden's nodes were also more frequent in females and were found to be associated to a highly significant degree with multiple osteo-arthritis affecting chiefly the interphalangeal joints of the fingers, the first carpometacarpal joints, the apophyseal joints of the spine, and the sacro-iliac joints.

A similar association between Heberden's nodes and multiple osteo-arthritis was demonstrated in males, but it was less marked in this sex, and in males both trauma and occupational stresses were shown to play an important role in determining both the site and the severity of osteo-arthritis and disk degeneration.

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### Ostéo-arthrite et dégénérescence du disque dans une population urbaine

#### RÉSUMÉ

On procéda à une enquête clinique et radiologique sur la fréquence des maladies articulaires dégénératives chez 380 personnes, âgées de 55 à 64 ans, constituant un échantillon d'une population.

Les indications antérieures, que la fréquence de la dégénérescence du disque intervertébral était relativement plus grande chez les hommes et celle de l'ostéo-arthrite chez les femmes, furent confirmées. On étudia les facteurs responsables de ces différences de sexe.

La fréquence plus grande de l'ostéo-arthrite chez les femmes était sans rapport avec métier, antécédents traumatiques ou signes de rhumatisme articulaire. L'obésité se trouvait plus souvent chez les femmes et était associée à une fréquence augmentée d'ostéo-arthrite des articulations d'appui, mais n'expliquait pas la fréquence élevée de l'ostéo-arthrite multiple des femmes. Les nodosités d'Heberden étaient aussi plus fréquentes chez les femmes et se voyaient associées dans une très grande mesure à un type d'ostéo-arthrite multiple attaquant surtout les articulations interphalangiennes des doigts, les carpo-métacarpiennes, les apophysaires vertébrales et les sacro-iliaques.

Une association similaire entre les nodosités de Heberden et l'ostéo-arthrite multiple fut trouvée chez les hommes, bien que à un degré moindre; on trouva aussi que le traumatisme et la fatigue professionnelle jouaient un rôle important dans la détermination du siège et de la sévérité de l'ostéo-arthrite et de la dégénérescence du disque.

### Osteoarthritis y degeneración discal en una población urbana

#### SUMARIO

Se hizo un reconocimiento clínico y radiológico de 380 personas de edad de 55 a 64 años, representando una muestra de una población urbana, con el fin de hallar la frecuencia de las enfermedades articulares degenerativas.

Se comprobaron los datos anteriores, que la frecuencia de la degeneración del disco intervertebral fué relativamente mayor en los hombres y la de la osteoarthritis en las mujeres. Se estudiaron los factores responsables de esta diferencia entre los sexos.

La frecuencia mayor de la osteoarthritis en las mujeres fué sin relación alguna con ocupación, antecedentes traumáticos o signos de reumatismo articular. La obesidad fué más frecuente en las mujeres, viéndose

asociada a una frecuencia aumentada de ósteoartritis de las articulaciones de apoyo, sin explicar la frecuencia aumentada de la osteoartritis múltiple de la mujeres. Las nudosidades de Heberden fueron también más frecuentes en las mujeres, asociándose a menudo al tipo de osteoartritis múltiple que ataca primeramente las articulaciones interfalángicas de los dedos, carpo-

metacarpeanas, apofisarias vertebrales y sacro-iliacas.

Una asociación similar, aunque menos pronunciada, entre nudosidades de Heberden y osteoartritis múltiple, fué encontrada en los hombres; se vió también que el traumatismo y la fatiga profesional desempeñaban un papel importante en la determinación del sitio y de la severidad de la osteoartritis y de la degeneración discal.



## TRIAMCINOLONE THERAPY IN RHEUMATOID ARTHRITIS

BY

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The introduction of cortisone as an anti-inflammatory agent stimulated the search for newer steroids with greater anti-rheumatic effect, but with fewer associated side-reactions. Shortly afterwards, hydrocortisone became available, and, although its anti-rheumatic effect was slightly greater, undesirable physiological responses were more or less similar. Fried and Sabo (1953) synthesized a corticosteroid analogue with a halogen atom at the 9 carbon position of the steroid nucleus called 9- $\alpha$ -fluoro-hydrocortisone. It was very much more potent than hydrocortisone, about ten times greater in anti-inflammatory effect, and with approximately 125 times the mineralocorticoid action (Liddle, Richard, and Tomkins, 1956; Boland, 1955). Marked sodium retention with this halogenated derivative precluded its application for practical use as an antiphlogistic agent in the treatment of rheumatoid arthritis, but it was of some value for patients with Addison's disease where the exaggerated mineralocorticoid effect was desirable.

In 1955, a very important chemical structural change resulted in the formulation of prednisone and prednisolone (Herzog, Nobile, Tolksdorf, Charney, Hershberg, Perlman, and Pechet, 1955) when a double bond was inserted between carbon atoms 1 and 2 of cortisone and hydrocortisone, respectively. These newer compounds were equally potent; they were approximately four times as great as their predecessors in glucocorticoid effect, whereas the mineralocorticoid action was diminished. In the usual maintenance dosages for treatment of rheumatoid arthritis, for example, electrolyte changes induced by these delta-1 analogues of cortisone and hydrocortisone proved no problem in clinical management of patients. However, other undesirable physiological reactions still occurred. In the hands of some investigators (Bunim, Pechet, and Bollet, 1955; Bollet, Black, and Bunim, 1955; Boland, 1956), complications with these latter

steroids, such as peptic ulceration, have been reported with even greater frequency.

In 1955 and 1956 a series of methylated corticosteroids were synthesized. Boland and Liddle (1957) reported that one of these, 6-methyl-prednisolone (Medrol), differed in no essential way from prednisolone itself. The sodium-retaining and potassium-losing activities of this compound were thought to be slightly less than those of prednisolone, but this was not definitely established. The hormone appeared to be at least as powerful as prednisolone in producing nitrogen-wasting; 41 patients with rheumatoid arthritis who received the drug as initial therapy showed no significant difference in degree or character of improvement from that anticipated with prednisone or prednisolone. Dosages were alike. Although the authors stated that their study was not sufficiently extensive properly to evaluate the complications of this new compound, they thought that most of the adverse reactions seen with the older preparations were also observed with 6-methyl-prednisolone.

Bernstein, Lenhard, Allen, Heller, Littell, Stolar, Feldman, and Blank (1956) synthesized a new preparation, by adding a 16- $\alpha$ -hydroxyl group to the 9- $\alpha$ -fluoro-prednisolone structure, and triamcinolone (16- $\alpha$ -hydroxyl-9- $\alpha$ -fluoro-prednisolone) was formulated. This compound eliminated the marked sodium-retaining potency of the previous analogue without diminution of glucocorticoid activity. Animal investigations (Perrine, Bell, Bortle, Heyder, Ross, and Ringler. In the press) revealed that triamcinolone was ten to forty times more active than hydrocortisone and three to twelve times more active than prednisolone in inducing glycogen deposition in fasted adrenalectomized rats. Diuretic and natriuretic potency exceeding that of prednisolone or hydrocortisone was also demonstrated in both adrenalectomized and normal animals. No hypertensive effect was observed in

rats. Haematological responses were similar to those noted with other steroids. The anti-inflammatory activity in inhibiting granuloma formation in rats was about ten times that of hydrocortisone.

Human metabolic studies (Hellman, Zumoff, Schwartz, Gallagher, Berntsen, and Freyberg, 1957; Freyberg, Berntsen, and Hellman, 1958) showed that triamcinolone caused a sodium diuresis, but no increased potassium excretion. The latter has been shown with long-term treatment and in acute metabolic studies with dosages as high as 30 mg. Preliminary information on calcium and phosphorus excretion and on nitrogen balance revealed relatively negligible changes in patients receiving 12 to 24 mg. of hormone daily. On very high doses, that is, over 50 mg. daily, losses of calcium, phosphorus, and nitrogen did take place. However, no general conclusions could be drawn on the influence of triamcinolone on nitrogen balance. A lesser tendency to cause peptic ulceration than other steroids was suggested by the preliminary findings of these investigators.

The encouraging animal and human studies on triamcinolone, particularly the possibility of decreased ulcerogenic effect and the lack of adverse mineralo-corticoid response, warranted further evaluation of this preparation. Our experiences with triamcinolone therapy in fifty patients with rheumatoid arthritis are reported below.

#### Procedure

The general plan for administering triamcinolone\* was similar to that employed with other anti-inflammatory steroids; that is, an initial suppressive dose was followed by gradual reduction to maintenance levels. Those patients receiving other steroids were switched to triamcinolone, with the same dose. Individuals not previously on such therapy were started on triamcinolone in total daily doses varying from 6 to 30 mg. Adjustments in dosages were made in small amounts, usually by 2 to 4 mg. and preferably at weekly intervals, until maintenance levels were attained. Early in the treatment with triamcinolone, when relatively large doses may have been administered, the dose was lowered more rapidly. After maintenance values were established, prednisone was substituted in many patients for comparative purposes. In a similar manner, the acetate and free alcohol forms of triamcinolone were compared by substituting one for the other, but without the patient's knowledge. The free alcohol form of triamcinolone was used for the major part of the study.

Other forms of therapy were continued without alteration. Most patients were simultaneously treated with gold salts and salicylates.

At each visit the patient's joints were evaluated subjectively for pain, stiffness, and range of motion, and objectively for the degree of synovitis as demonstrated by the amount of heat, swelling, capsular thickening, fluid, tenderness, and range of motion. These were estimated and recorded as a composite percentage value, 100 per cent. indicating maximum improvement.

The duration of observation varied, but it was continued for more than a year in fifteen subjects; 34 cases were studied for more than 6 months, and only six for less than 2 months.

Clinical evidence of toxicity was sought at each visit. Observations were made of moon facies, hirsutism, ecchymoses, blood pressure changes, body weight, and particularly of gastro-intestinal disturbances. Other possible complications were also recorded.

Laboratory procedures included urine analysis, complete blood count, and erythrocyte sedimentation rate (Westergren), at least once monthly and more frequently when the patient was first placed on a new medication. Electrolyte determinations for sodium, potassium, and chloride, and fasting blood sugars were done throughout the study.

Gastric analyses were performed serially on fourteen patients according to the technique of Kirsner and Ford (1955). Histalog in a dose of 0.5 mg./kg. body weight was used to stimulate the gastric mucosa. Eight specimens of gastric juice were obtained at 15-minute intervals during the test, four before histalog stimulation, and four afterwards. Volume, concentration in clinical units of free acidity, and mg. hydrochloric acid were determined for each specimen. A total of 38 gastric analyses were done. Barium meals were performed serially during therapy in twelve of the above patients, and also in twelve others. Nine patients had gastric mucosal biopsies using the Wood's technique (Joske, Finckh, and Wood, 1955).

#### Results

The free alcohol and acetate forms of triamcinolone were compared in eighteen individuals. No significant difference was demonstrated between these preparations in anti-inflammatory response. The dosages used for each were generally the same, only an occasional patient requiring a slightly higher dose of one drug or the other. A limited supply of the acetate derivative did not permit long-term comparisons of side-reactions, but no disparities were noted during the short period of observation.

The initial higher dosage of triamcinolone was lowered to maintenance levels without difficulty. The maintenance dose averaged 7.9 mg., but there were wide variations from 2 to 24 mg. daily.

The anti-inflammatory response to triamcinolone was very satisfactory. All but four patients demonstrated significant improvement (i.e. greater than 50 per cent.). In only one instance was there no anti-inflammatory response. The alleviation of

\* The triamcinolone used in this study was supplied as Aristocort by Lederle Laboratories Division, American Cyanamid Company, Pearl River, N.Y.

rheumatic manifestations was similar to that observed with other steroids as regards rapidity, degree, and duration of improvement. A few patients still preferred triamcinolone to prednisone or prednisolone for its anti-rheumatic effect, although there was no objective evidence to corroborate this impression. The dose of triamcinolone was approximately 80 per cent. that of these latter compounds as evaluated in fifteen patients.

White blood cell counts increased during therapy in the majority of instances. The erythrocyte sedimentation rates diminished in the same way as with earlier steroids. The urine analyses were normal. The electrolyte determinations of sodium, potassium, and chloride (performed 43 times in seventeen patients at various times during the study) revealed no significant alterations. Acute studies were not done with initial dosages. The fasting blood sugar was unchanged in twenty patients on whom a total of 61 tests were made. In several cases there were four, five, or six determinations of the fasting blood sugar. In three individuals, fasting sugars were elevated on one occasion, but subsequent re-checking revealed normal values. Diabetes did not result in any subjects.

Many adverse physiological reactions occurred (Table I), particularly moon facies and buffalo humping which developed in 24 patients. Ecchymoses were recorded in sixteen. Hirsutism was prominent and was associated with moon facies in twelve patients. It was not possible to compare these side-effects exactly with those of previous steroids in these patients because the duration of observation with the other hormones was not sufficiently long.

An initial weight loss of 2 lb. or more during the first week's therapy occurred in sixteen of 37

patients checked. In two of these the loss was considered coincidental because of similar variations in past weeks on other medications. Nineteen of this group had originally been switched from prednisone or prednisolone to triamcinolone, with seven demonstrating a like diminution in weight. Weight loss of 2 lb. or more occurred in nineteen subjects over the entire period of study. Loss of 10 lb. or more occurred in seven cases (maximum 27 lb.). In fifteen patients after triamcinolone therapy for varying periods, prednisone was substituted for intervals of a few days to 1 month. Seven of this group then showed an increase in weight of 2 lb. or more. Nine patients gained weight during triamcinolone therapy.

Increased appetite occurred in eleven patients and anorexia in ten, with two of the former group later developing anorexia. Other gastro-intestinal symptoms (bloating, excess gas, nausea, epigastric burning, etc.) were observed in fifteen subjects. One patient had much bloating while taking prednisone, but this was less marked with triamcinolone. Another had had a disturbingly increased appetite while taking the earlier steroids, and found triamcinolone more satisfactory because the appetite returned to normal.

The effect of triamcinolone on gastric-juice production was studied in fourteen patients (8 male\* and 6 female). Three patients were evaluated during therapy extending over approximately a year, and a fourth patient for over 200 days. Control histalog gastric analyses were performed in thirteen individuals, ten during a period of no steroid therapy, and three during prednisone administration. One patient had no control analysis. The results are summarized in Table II (opposite), showing volume, concentration in clinical units, and total mg. hydrochloric acid. The four specimens before histalog stimulation and the four following are totalled and listed under the Basal and Histalog columns respectively. The figures suggest a slight trend towards an increase in gastric juice or hydrochloric acid formation in five or six cases in the post-histalog period, but no consistent alteration was produced. The various gastric analyses performed during triamcinolone administration revealed no constant change when compared with the prednisone or no steroid control periods. Nor was there any difference in the effect of the acetate and free alcohol forms of triamcinolone in this limited trial. The results were very variable from patient to patient and even on different occasions in the same individual.

TABLE I  
HORMONAL EFFECTS OF TRIAMCINOLONE THERAPY  
IN FIFTY PATIENTS WITH RHEUMATOID ARTHRITIS

Reaction	Number of Patients
Moon Facies .. .. .	24
Final Weight Loss .. .. .	19
Ecchymoses .. .. .	16
Nausea, Gas, Bloating, Epigastric Distress .. .. .	15
Initial Weight Loss .. .. .	14
Hirsutism .. .. .	11
Increased Appetite .. .. .	11
Anorexia .. .. .	10
Weight Gain .. .. .	9
Muscle Cramps .. .. .	7
Flushes .. .. .	6
Erythema .. .. .	3
Dizziness .. .. .	3
Acne .. .. .	3
Headache .. .. .	2
Weakness .. .. .	2
Gastric Ulcer .. .. .	1
Osteoporosis and Fracture .. .. .	1

\* Case 14 (Table II) did not have rheumatoid arthritis.



TABLE II  
RESULTS OF GASTRIC ANALYSES DURING TRIAMCINOLONE THERAPY  
IN PATIENTS WITH RHEUMATOID ARTHRITIS

Patient No.	Sex	Age (yrs)	Date	Drug†	Average Total Daily Dose (mg.)	Duration of Therapy (days)	Basal*			Histalog*		
							Vol. (ml.)	Cl.U.	Output† (mg.)	Vol. (ml.)	Cl.U.	Output† (mg.)
1	F	64	3.4.57	Pred	8	740	65	0	0	49	0	0
			23.4.57	Tdac	4	8	37	0	0	76	6.3	2.19
			21.5.57	Tdac	6	25	54	0	0	48	0	0
			26.3.58	TOH	4	340	92	0	0	83	8	22.6
2	F	62	1.4.57	Pred	13	150	39	17.0	24.2	77	56	158.1
			16.4.57	Tdac	12	8	52	40.5	76.8	51	92	335.8
			17.5.57	Tdac	10	30	50	24.0	15.94	83	89	150.1
			18.6.57	TOH	10	72	25	8.5	4.0	61	63.5	83
3	M	67	8.5.57	Pred	15	23	—	4	—	—	25	—
			5.11.57	TOH	5	43	127	49.0	229	145	74	309.0
			2.5.58	TOH	6	221	—	5	—	—	0	—
4	F	54	10.4.57	Tdac	8	51	—	32	—	—	98	—
			24.4.57	Tdac	8	61	61	89	127.5	145	112.5	215.8
			24.5.57	Pred	10	18	36	14	6.5	57	0	0
			19.3.58	TOH	10	390	34	14	7.8	124	76.0	110.7
5	F	63	25.4.57	None	—	—	12.5	11.5	5.4	43	29	48.6
			10.6.57	Tdac	8	14	47	0	0	40	0	0
			11.2.58	TOH	8	273	53	4.5	0	99	40	144.5
6	F	58	29.3.57	None	—	—	74	12	37.0	115	63.0	182.4
			12.4.57	Tdac	12	11	45	21	52.0	226	67.0	809.0
			3.5.57	Tdac	12	32	54	0	0	61	0	0
7	M	62	17.2.58	None	—	—	92	30	18.7	143	41	312.0
			16.4.58	TOH	8	56	83	25	186	164	76	1,040.0
8	F	50	15.1.58	None	—	—	75	—	—	99	25	209.0
			4.3.58	TOH	16	28	30	5	23	222	14	301.0
9	M	45	22.1.58	None	—	—	72	35	174	175	57	437.5
			20.2.58	TOH	16	25	84	26	150	272	65	625
10	M	45	10.12.57	None	—	—	48	0	0	178	57	273
			23.12.57	TOH	8	5	63	0	0	128	38	413
11	F	56	18.2.58	None	—	—	25	0	0	45	51	86
			8.4.58	TOH	8	49	35	20	18	73	46	124
12	M	53	22.1.58	None	—	—	98	0	0	83	4	12.4
			17.2.58	TOH	16	14	165	4	24	163	17	99.7
13	M	35	15.3.58	None	—	—	228	0	0	145	0	0
			26.3.58	TOH	16	12	126	0	0	106	4	11.7
14	M	80	19.1.58	None	—	—	70	37	95.6	194	49	468
			28.1.58	TOH	8	12	—	—	—	239	60	502

\* These values are the combined figures for the four specimens before and after histalog stimulation respectively.

† Output equals Volume × Clinical Units × 0.00365 × 10.

‡ Pred = Prednisone acetate.

Tdac = Triamcinolone diacetate.

TOH = Triamcinolone (alcohol).

Roentgenograms of the upper gastro-intestinal tract were performed in 24 patients during triamcinolone therapy, including twelve of the above group. Approximately half also had control films.

Patient 1 (Table III, overleaf) developed a peptic ulcer located on the lesser curvature of the stomach which appeared after 9 months on maintenance doses averaging 9 mg. daily. The ulcer healed without difficulty while steroid therapy was continued as before, and antacids, an ulcer diet, sedation, and anticholinergics were added to the regime. Patient

13 (Table III), who had an asymptomatic "scarred duodenal bulb" on the control barium meal, revealed no change with a repeat examination 3½ months later. Patient 14 (Table III), who had a scarred duodenal bulb before the study, showed no evidence of this subsequently. Patient 18 (Table III) had two gastric ulcers from prednisone therapy when he was switched to maintenance doses of triamcinolone with the addition of the anti-ulcer regime mentioned above; the ulcers healed within 10 weeks as established by gastroscopy, x-ray



TABLE III

CORRELATION OF DURATION OF TREATMENT AND DOSE  
OF TRIAMCINOLONE WITH BARIUM MEALS IN  
24 PATIENTS WITH RHEUMATOID ARTHRITIS

Patient No.	Duration of Therapy at Time of Last Barium Meal (days)	Average Daily Maintenance Dose (mg.)	Results of X Ray
1	435	8	Gastric ulcer after 9 months; subsequently healed
2	178	6	Negative
3	525	9	Negative
4	198	9	Negative
5	154	11	Negative
6	316	9	Negative
7	333	4	Negative
8	260	5	Diverticulum of stomach
9	400	16	Negative
10	460	8	Negative
11	383	6	Negative
12	159	6	Negative
13	109	6	Scarred duodenal bulb in control; no subsequent change
14	198	7	Scarred duodenal bulb in control; negative subsequently
15	367	3	Negative
16	283	8	Negative
17	185	22	Negative
18	105	8	Gastric ulcers with prednisone; healed during triamcinolone therapy
19	305	14	Negative
20	93	12	Negative
21	103	12	Negative
22	77	8	Negative
23	80	9	Negative
24	106	9	Negative

examination, and clinical evaluation of symptoms. Patient 8 (Table III), who had severe rheumatoid arthritis with a gastric diverticulum, had a gastrointestinal haemorrhage after receiving triamcinolone for 8 months in doses averaging 5 mg. daily. The site of bleeding was not established despite x-ray studies and gastroscopy, but the haemorrhage ceased spontaneously in a few days, and triamcinolone was restarted after temporarily discontinuing its use.

Table III correlates the average maintenance dose and the duration of therapy with the results of the last barium meal. In most instances, x-rays were obtained after 6 months' treatment.

Gastric mucosal biopsies were taken in nine patients. Eight had both control biopsies and repeat procedures after 2 weeks of triamcinolone therapy in dosages averaging 12 mg. daily. The ninth was the patient with the gastric diverticulum and bleeding in whom a biopsy was performed after the source of haemorrhage was not elucidated by x-ray and gastroscopy. This biopsy was also non-revealing. None of the sections showed any significant difference from the controls when examined with the haematoxylin-eosin stain. One

patient had chronic gastritis in both the control and follow-up.

Muscle cramps occurred in seven patients, three of whom had had similar episodes before this therapy. Erythema of the face and chest was noted in three cases, and flushes in six. All of the latter patients were in the menopausal age group or older. Headaches occurred in two, one of whom had taken prednisone without similar difficulty. Weakness was also present during prednisone administration in one out of two patients with this complaint. Acne, which had been present as a result of previous prednisone treatment in two cases, gradually disappeared on triamcinolone. In both these instances the dose of triamcinolone was lower than the earlier steroid dose. Mild acne developed in three other cases. Osteoporosis with fracture of a lumbar vertebra occurred in one individual. Episodes of severe lower back pain in two additional subjects did not prove to be due to osteoporosis or fracture on x-ray examination. There were no elevations of blood pressure. Neither psychosis nor euphoria was observed.

Several findings, possibly related to triamcinolone therapy but more likely coincidental occurrences, are listed in Table IV. Alopecia in each of the two instances happened in elderly women and was localized to the scalp where its distribution was generalized. One patient had three episodes of syncope after 8 months of therapy with maintenance doses averaging 22 mg. daily. No similar experiences had occurred before or since, although the medication was continued for an additional 2 months. Superficial thrombophlebitis was found in three patients; this was evanescent and disappeared within 1 to 2 weeks, and no serious complications resulted. Three patients developed herpes zoster. Blanching of the fingers became a prominent finding after 3 months of triamcinolone therapy to a 25-year-old white female who was maintained on doses averaging 8-12 mg. daily; the Raynaud's phenomena grew progressively worse in the ensuing 2 months, while the steroid dosage was gradually reduced to nothing. Gangrene developed at the tip of one

TABLE IV  
QUESTIONABLE HORMONAL EFFECTS OF TRIAMCINOLONE IN FIFTY RHEUMATOID PATIENTS

Reaction	Number of Patients
Superficial Thrombophlebitis .. ..	3
Herpes Zoster .. ..	3
Alopecia .. ..	2
Syncope .. ..	1
Periarteritis with Raynaud's Phenomenon .. ..	1

finger, and a muscle and skin biopsy from a clinically uninvolved area revealed a marked inflammatory reaction in the blood vessels of both tissues indicative of a periarteritis. The walls of small arteries, arterioles, and capillaries were infiltrated with polymorphonuclear leucocytes and lymphocytes, and in some areas showed necrosis. It could not be determined whether this was a primary reaction or secondary to steroid therapy.

Triamcinolone was discontinued after varying periods of treatment in seventeen patients for the reasons listed in Table V. In six this was necessitated by complications; patient contact was lost in seven; and the treatment was no longer needed in four. The one death which occurred was unrelated.

TABLE V  
REASONS FOR DISCONTINUATION OF  
TRIAMCINOLONE THERAPY

Cause	Number of Patients
Loss of Contact with Patient .. ..	7
No Further Need for Steroid .. ..	4
Osteoporosis with Fracture .. ..	1
Inadequate Improvement .. ..	1
Deceased .. ..	1
Anorexia and Weight Loss .. ..	1
Periarteritis .. ..	1
Gastro-Intestinal Haemorrhage .. ..	1

### Discussion

Triamcinolone was found to be a very effective anti-rheumatic agent. The anti-inflammatory effect was slightly greater than that of prednisone or prednisolone in a dosage ratio of approximately 4 to 5. In a few patients triamcinolone was preferred to the latter drugs. The acetate and free alcohol forms of triamcinolone were interchangeable without noticeable effect.

Many undesirable side-effects of triamcinolone therapy were comparable to those of other anti-inflammatory glucocorticosteroids. Moon facies, hirsutism, and ecchymoses seemed to be at least as prevalent as with the older preparations. Gastro-intestinal complaints of nausea, gas, bloating, anorexia, or epigastric distress were not unusual. Anorexia which would be a disadvantage in most instances could also serve a useful purpose by aiding weight reduction in obese cases. In addition, patients with a disturbingly increased appetite from previous steroids might find this lack of stimulation of appetite a very desirable feature. Such was the case in one patient. It should be mentioned that increased appetite occurred about as often as anorexia, and that weight gain was not infrequent. The latter could be attributed to the stimulation of

appetite or to the increased sense of well-being which fostered better eating. Weight gain was not due to fluid retention.

Of great interest was the weight loss which occurred in some individuals. The initial loss might be explained by depletion of fluids due to sodium diuresis which was previously demonstrated with triamcinolone (Hellman and others, 1957; Freyberg and others, 1958). Explanation of weight loss progressing with long-term therapy was not clear; continuing diuresis was not likely. Anorexia which was a problem in several patients might have been partially responsible because of decreased food intake. For those individuals without anorexia, nitrogen wasting secondary to steroid therapy would appear to be the likely explanation, although adequate proof was lacking at this time. Early metabolic studies showed no nitrogen loss (Hellman and others, 1957), but later investigations (Freyberg and others, 1958), utilizing large doses of steroid indicated that catabolism did occur. The one instance of osteoporosis with fracture in this series, and the relative infrequency of this occurrence in other reports, suggested that factors other than negative nitrogen balance might play a part. However, it should be realized that x-ray evidence of negative nitrogen balance as demonstrated by demineralization of bone does not appear early, and that the studies thus far reported have been of relatively short duration for this manifestation. Chronic dehydration (Freyberg and others, 1958) and negative electrolyte balance (Curd and Spurr, 1958) have been proposed as additional factors in this weight loss.

The possibility of a decreased ulcerogenic potential for triamcinolone requires further observation for affirmation. Development of a gastric ulcer in only one of 24 patients examined roentgenographically supports other encouraging reports in this regard (Hellman and others, 1957; Freyberg and others, 1958; Dubois, 1958). The healing of the ulcer in this patient and of two gastric ulcers due to previous prednisone therapy in another who was treated simultaneously with triamcinolone and an anti-ulcer regimen, corroborate the impression of a decreased ulcerogenic stimulus. Caution in interpretation is warranted, however, since ulcers have also been observed to heal during the administration of other steroids.

Gastric analyses suggested increased gastric-juice production in the post-histalog specimens in a few instances. When these results were compared with the figures given for normal controls (Kirsner and Ford, 1955), they were found to fall into the normal range for the age and sex of the patients involved,

and their significance was, therefore, questioned. The effect of triamcinolone on gastric-juice formation was not consistent; and, in fact, any response would be difficult to prove by the analyses obtained from our patients.

Since the gastric biopsy utilizing the Wood's technique was a blind procedure, the specimens obtained during triamcinolone therapy in the nine patients studied were not necessarily from the same area of the stomach as those from the controls. Nevertheless, no alteration in histological structure was apparent.

Interesting side-reactions which might be peculiar to triamcinolone were erythema of the face and neck, flushes, headache, and dizziness. Explanations for these manifestations are wanting.

The absence of diabetes in this series would bear further observation, but a diabetogenic effect has been noted by other investigators (Freyberg and others, 1958).

The diminished mineralocorticoid action obviated the problem of sodium retention. Electrolyte determinations revealed no abnormalities for the dosage range used.

These studies indicate that triamcinolone may be satisfactorily employed in the treatment of rheumatoid arthritis. Since this addition to the armamentarium of anti-inflammatory steroids may offer certain advantages, its use should prove of benefit to many patients. However, undesirable physiological reactions should also be considered; this applies to the other anti-rheumatic steroids as well. The physician to-day, having several of these preparations to choose from, should carefully weigh the advantages and disadvantages of each before prescribing for his patient.

### Summary

Triamcinolone was administered to fifty patients with rheumatoid arthritis and gave a satisfactory anti-rheumatic response. The maintenance dose averaged 7.5 mg. daily. This compound was more potent than prednisone or prednisolone in a dosage ratio of 4 to 5. Comparison of the acetate and free alcohol forms of triamcinolone revealed no significant difference. Most of the cushingoid-type reactions complicating other steroid therapy occurred with triamcinolone with equal or greater frequency. The ulcerogenic effect of this preparation may be minimal, as only one patient out of 24 x-rayed revealed gastric ulceration. Studies of gastric-juice production in fourteen patients showed no consistent change which could be considered due to hormone administration. Gastric biopsies in nine patients were also non-revealing. Other

physiological effects, such as anorexia, weight loss erythema of the chest and face, flushes, headache and dizziness, may be peculiar to triamcinolone. Diabetes did not occur. This last observation merits further evaluation.

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### Traitement à la triamcinolone de l'arthrite rhumatismale

#### RÉSUMÉ

On administra de la triamcinolone à 50 malades atteints d'arthrite rhumatismale et la réaction anti-rhumatismale fut satisfaisante. La dose moyenne de soutien fut de 7,5 mg. par jour. Ce composé fut 4 à 5 fois plus puissant, dose pour dose, que la prednisone ou la prednisolone. On ne trouva pas de différence appréciable entre l'acétate et l'alcool libre de la triamcinolone. La plupart des réactions du type "Cushing", qui compliquent la thérapie par d'autres stéroïdes, se produisit aussi avec la triamcinolone avec une fréquence similaire ou plus grande. L'effet ulcérigène de ce produit peut être minime, car un seul malade sur 24 radiographiés révéla une ulcération gastrique. L'examen de la sécrétion du suc gastrique chez 14 malades ne révéla pas d'altérations définies attribuables à l'administration de l'hormone. Des biopsies gastriques chez 9 malades donnèrent également un résultat négatif. D'autres effets physiologiques, tels que anorexie, amaigrissement, érythème de la poitrine et du visage, bouffées de chaleur, céphalée et vertige pourraient être particuliers à la triamcinolone. Il n'y eut pas de diabète. Cette dernière observation demande une vérification ultérieure.

### Tratamiento con la triamcinolona de la artritis reumatoide

#### SUMARIO

Triamcinolona fué administrada a 50 enfermos con artritis reumatoide, obteniéndose una reacción anti-rumática satisfactoria. La dosis media de sostén fué de 7,5 mg. diarios. Este compuesto se reveló 4 o 5 veces más fuerte, en dosis iguales, que la prednisona o la prednisolona. No se encontró diferencia apreciable

entre el acetato y el alcohol libre de la triamcinolona. La mayoría de las reacciones del tipo "Cushing", que suelen complicar la terapia con otros esteroides, ocurrieron también con la triamcinolona con una frecuencia igual o superior. El efecto ulcerígeno de este producto parece mínimo, ya que un solo enfermo de 24 radiografiados reveló una ulceración gástrica. La investigación de la secreción del jugo gástrico en 14 enfermos

no reveló alteraciones que se pudieran atribuir a la administración de la hormona. Biopsias gástricas en 9 enfermos dieron también un resultado poco revelador. Otros efectos fisiológicos, como anorexia, pérdida de peso, eritema del pecho y de la cara, rubores, jaqueca y vertigo podrían ser particulares a la triamcinolona. No hubo diabetes. Esta última observación necesita una verificación ulterior.



## NATURE OF ANAEMIA IN RHEUMATOID ARTHRITIS

### IV. EFFECTS OF THE INTRAVENOUS ADMINISTRATION OF SACCHARATED OXIDE OF IRON

BY

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In previous communications the characteristics of the anaemia and abnormalities in the metabolism of iron in patients suffering from rheumatoid arthritis have been described (Roy, Alexander, and Duthie, 1955; Richmond, Gardner, Roy, and Duthie, 1956). The most important results of these investigations may be briefly summarized: the existence of moderate hypochromia of the red cells was confirmed; there was a significant degree of hypoferraemia, but unlike the finding in simple iron deficiency anaemia, the total iron binding capacity of the plasma was normal; no evidence of impaired absorption of iron from the gut was obtained, an observation substantiated by Jeffrey, Freundlich, Jackson, and Watson (1955) using radioactive iron; the rate of removal of saccharated oxide of iron (S.O.I.) from the plasma after intravenous administration was more rapid in patients suffering from rheumatoid arthritis than in healthy individuals. In a study of 61 patients, stainable iron (Prussian blue method) was absent from the marrow, or present only in very small quantities, in 49 per cent. of cases. The normoblast count in the marrow varied directly with the haemoglobin level in the blood, suggesting a failure on the part of the marrow to respond to the anaemia. A highly significant correlation was found to exist between the degree of anaemia and the erythrocyte sedimentation rate. No relationship could be demonstrated between the haemoglobin level (Hb), red cell count (R.B.C.), mean corpuscular haemoglobin concentration (M.C.H.C.), or plasma iron level, and the iron content of the bone marrow.

Alexander, Richmond, Roy, and Duthie (1956), using the Ashby technique of differential agglutination, showed that erythrocytes from healthy donors were eliminated from the circulation with abnormal rapidity in patients with rheumatoid arthritis, although erythrocytes from rheumatoid donors survived rather longer in rheumatoid recipients. Despite absence of the usual signs of blood destruction (reticulocytosis, increased amounts of bilirubin

in the serum, and urobilinogen in the urine), these findings suggested that a haemolytic process was one factor in the causation of the anaemia. This haemolytic process appeared to be uninfluenced by the administration of corticotrophin in doses sufficient to suppress the clinical signs of the disease.

#### Use of Saccharated Oxide of Iron

The role of iron in the aetiology of the anaemia of rheumatoid arthritis has proved difficult to evaluate. Several workers (Sinclair and Duthie, 1949, 1950; Ross, 1950; Jeffrey, 1952, 1953a, 1953b; Millard and Barber, 1956; McCrea, 1958) have shown that the administration of saccharated oxide of iron (S.O.I.) intravenously produces a satisfactory rise in the haemoglobin level in a varying proportion of cases. Using doses of 1 g., Jeffrey (1952) suggested that response occurs most frequently in patients with co-existing iron deficiency as evidenced by a raised total iron-binding capacity, low plasma iron, and low mean cell haemoglobin concentration. This view is supported by the results of McCrea (1958), which show that, of his eleven patients who had a "significant" response (a rise in haemoglobin level or more than 2 g./100 ml.), all but one had no stainable iron in the marrow and in only two could no cause for simple iron-deficiency be found.

Sinclair and Duthie (1950) noticed a fall in the erythrocyte sedimentation rate (E.S.R.) in many of their cases who responded to intravenous S.O.I. This observation had led to the suggestion that clinical improvement after hospital treatment, unrelated to the use of S.O.I., may have led to an improvement in the anaemia. Our previous experience does not confirm this view, and it would seem equally likely that the clinical improvement frequently observed during treatment with S.O.I. may be attributable to some action other than a direct effect on haemopoiesis.

For these reasons it was considered important to undertake a further assessment of the value of

S.O.I. in rheumatoid arthritis. The object of the present paper is to report the results of a controlled therapeutic trial. In previous studies 1 to 2 g. S.O.I. have been given and up to 60 per cent. of patients have shown some improvement. In view of the possibility that a higher proportion of cases might respond if larger doses were given, the treated group in the present study were given a total of 5 g. S.O.I. The initial iron content of the bone marrow, the findings in the peripheral blood, the clinical status of the patients throughout the period of observation, and, in some cases, the rate of clearance of S.O.I. during the period of its administration have been recorded.

### Material

46 hospital patients were admitted to the trial. The diagnosis of rheumatoid arthritis had been established in each patient on clinical and radiological grounds, and all were undergoing the same basic regimen of treatment (rest, salicylates, splintage, and physiotherapy). Only patients in whom there was no known cause for anaemia other than rheumatoid arthritis were included. 26 cases were placed in the group to be treated and twenty in the control group by random allocation. The composition of the groups with regard to sex, age and duration of disease is shown in Table I.

TABLE I

COMPOSITION OF TREATED AND CONTROL GROUPS

Group		Treated	Control
Number of Patients		26	20
Sex	Male	10	7
	Female	16	13
Age Distribution (yrs)	20-39	2	2
	40-59	13	12
	60-79	11	6
	Mean	56.4	53.5
Duration of Disease (yrs)	Under 2	4	2
	2-10	14	9
	Over 10	8	9
	Mean	7.95	9.10

### Methods

Each patient was observed in hospital for a period of approximately 2 weeks before being allocated to one of the two groups. During this time the activity of the disease and the functional capacity of each patient were assessed, the basic regimen of treatment was established, and the peripheral blood (Hb, R.B.C., P.C.V., E.S.R.) was examined on two or three occasions. In addition, the plasma iron concentration was estimated and bone marrow was obtained for a study of its iron content.

In the cases allotted to the treatment group, S.O.I. was administered intravenously in a dose of 200 mg. daily to a total of 5 g. In the treated and the control groups, the peripheral blood was examined each week during the period in hospital (usually 6 to 8 weeks) and the plasma iron was measured at regular intervals. Thereafter all patients were reviewed in respect of changes in the activity of the disease, functional capacity, peripheral blood findings, and plasma iron levels, one month and 3 months after the course of S.O.I. in the treated group, and at similar intervals after discharge from hospital in the control group.

*Disease Activity and Functional Capacity.*—The criteria for grading functional capacity and disease activity were those used by Duthie, Brown, Knox, and Thompson (1957), and are reproduced in Tables II and III.

TABLE II

GRADES OF FUNCTIONAL CAPACITY

Grade	Definition	Remarks
I	Fit for all normal activities	Full employment in usual work Full house duties
II	Moderate restriction	Usual employment with modifications Light or part-time work All housework save the heaviest No dependency on others
III	Marked restriction	Only very light work or light housework Some degree of dependency on others
IV	Confined to chair or bed	Not capable of any work Completely dependent on others

TABLE III

GRADES OF DISEASE ACTIVITY

Grade	Degree of Activity	Erythrocyte Sedimentation Rate (mm./hr)	Haemoglobin (per cent.)	Joint Involvement	Systemic Disturbance
1	Inactive	20 or Under	85 or Over	No symptoms due to inflammation in the joints	None
2	Moderately Active	20-60	65-85	Signs of activity in several joints	Moderate, weight steady
3	Very Active	Over 60	65 or Under	Signs of acute inflammation in many joints	Marked, with loss of weight

**Peripheral Blood Examination.**—The methods for estimating Hb, R.B.C., P.C.V., E.S.R., and plasma iron concentration were the same as those described in earlier papers (Roy and others, 1955; Richmond and others, 1956). Haemoglobin values were recorded on the scale 100 per cent. = 14.3 g./100 ml.

**Iron Content of Bone Marrow.**—In 36 cases (nineteen in the treated group and seventeen controls) the iron content of the bone marrow was estimated by one of us (D.L.G.) using the technique described by Richmond and others (1956). In 26 subjects (fourteen in the treated group and twelve controls) the marrow iron was measured chemically (Kerr, 1957).

**Rate of Clearance of S.O.I.**—In eleven patients in the treated group, the rate of clearance from the blood of a single dose of 200 mg. S.O.I. was measured at the start of the course, after a total of 2 g. had been given, and again at the end.

**Comparison of Treated and Control Groups at Start of Trial.**—The treated and control groups were similar in respect of age, sex, and duration of disease (Table I). The iron content of the bone marrow in each group was comparable (Table IV). At the start of the trial the differences between the grades of functional capacity and disease activity and the E.S.R. in the two groups were not significant (in each case  $p > 0.1$ ). The initial mean haemoglobin level was significantly lower in the treated group than in the controls ( $p < 0.05$ ). Full consideration has been given to the influence which this difference might have had on the results of the investigation. The relationship between the initial Hb level and the subsequent improvement in Hb was calculated in the control group. In estimating the increment in Hb which might have been expected in the treated group on the basis of this calculation, it was found that the improvement which actually occurred after the administration of S.O.I. far exceeded that which could have been explained by the relatively lower Hb level in this group at the start of the trial.

When the initial data from all 46 patients in the trial were considered, it was confirmed that the severity of the anaemia varied directly with the activity of the disease as measured by the E.S.R.

( $p < 0.05$ ). There was a highly significant relationship between the Hb level and the M.C.H.C. ( $p < 0.001$ ). As had been previously noted, no correlation existed between the Hb, the plasma iron concentration, and the iron content of the bone marrow.

The clinical and laboratory data from all the patients studied in the trial are presented in the Appendix.

## Results

### Changes following Administration of S.O.I.

**Hb, R.B.C., and M.C.H.C.**—The mean haemoglobin level in the treated group showed an increase from an initial value of 73.1 to 91.9 per cent. 1 month after the last injection. The mean level was maintained at 3 months. All the cases in the treated group had improved at the one month assessment and after 3 months the Hb had fallen below the pre-treatment level in only two cases. In sixteen cases the Hb increased by more than 14 per cent. (2 g./100 ml.), in eight cases by 7 to 14 per cent. (1.2 g./100 ml.), and in only two by less than 7 per cent. An examination of results in individuals showed that sixteen patients had attained their maximum response by 1 month, and that the remaining ten patients reached the highest haemoglobin level between 1 and 3 months after the last injection of S.O.I.

In the control group the mean Hb level was initially 79.1 per cent., at 1 month 82.0 per cent., and at 3 months 83.9 per cent. In only two patients in this group did the increase in haemoglobin during the period of observation exceed 14 per cent.

The difference between the improvement in the treated and control groups was significant ( $p < 0.01$ ). This is illustrated in the Figure (opposite).

When the mean values of the haematological indices in the treated and control groups are compared (Appendix), it appears that the better response of the treated group was not due to correction of the M.C.H.C., the change in the M.C.H.C. being small and of the same order in both groups.

TABLE IV  
IRON CONTENT OF BONE MARROW IN TREATED AND CONTROL GROUPS

Method of Assessment		Iron Content of Bone Marrow				
		Prussian Blue			Chemical	
		Total	Nil and Trace	+ and ++	Total	Mean Value (mg./100 g. Protein)
Group	Treated	19	11	8	14	55 ± 28
	Control	17	10	7	12	43 ± 17

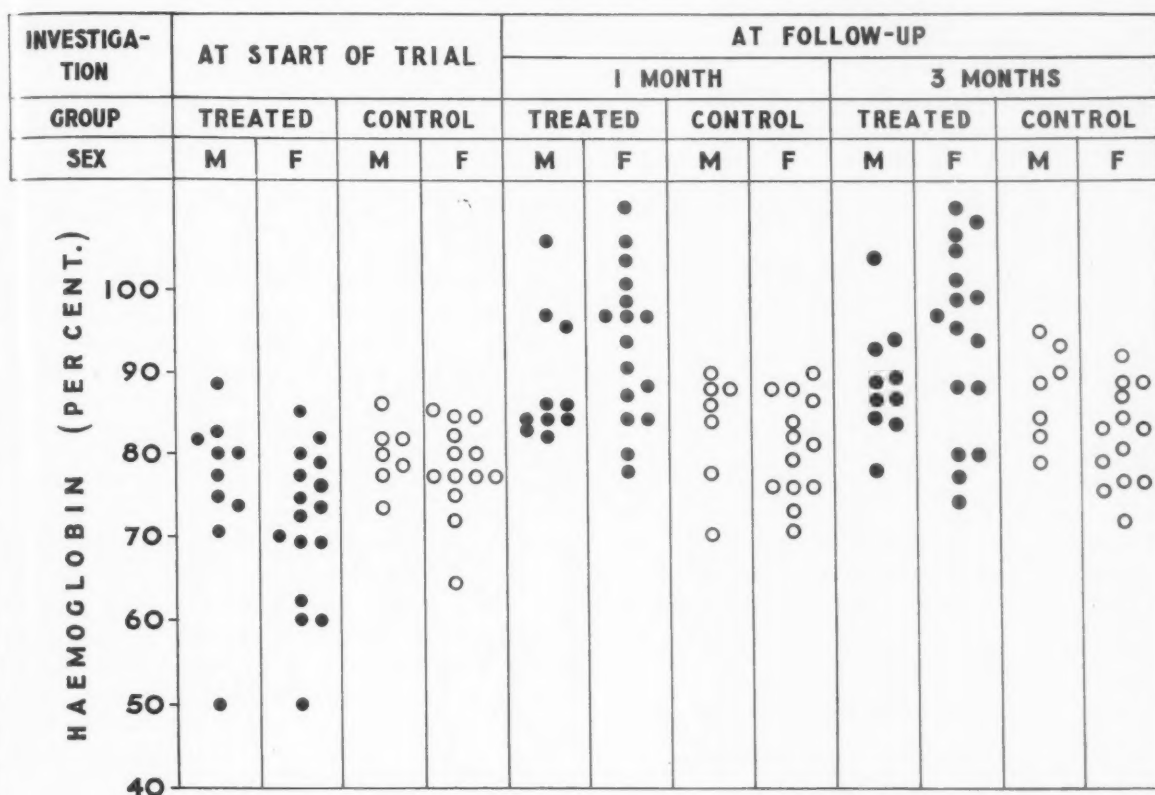


Figure.—Improvement in haemoglobin levels in treatment and control groups, by sex.

The improvement observed in the patients receiving S.O.I. seems to be attributable mainly to a rise in the red cell count. In the treated group the mean R.B.C. count was higher than the initial value by 13.5 per cent. after 1 month and by 12.5 per cent. after 3 months. In the controls the comparable figures were 1 per cent. in each case.

The data given in the Appendix show that, in eight patients in the treated group, the initial haemoglobin level was 70 per cent. or lower. As only one of the controls had such a low haemoglobin level,

it was decided to examine the character and response of the anaemia in these patients in further detail. The results are presented in Table V, which shows that the patients presenting with a haemoglobin level of 70 per cent. or less (Group I) differed from the remainder of the treated group (Group II) in several respects.

The mean initial R.B.C., M.C.H.C., and M.C.V. in the patients in Group I were consistently lower than those recorded in the remainder of the treated group. Analysis of the response to S.O.I. reveals

TABLE V  
RELATIONSHIP OF HAEMATOLOGICAL INDICES AND PLASMA IRON TO INITIAL HAEMOGLOBIN LEVEL IN TREATED GROUP

Group	I Initial Hb 70 per cent. or Less (8 patients)			II Initial Hb 71 per cent. or More (18 patients)		
	Before Treatment	1/12 Follow-up	3/12 Follow-up	Before Treatment	1/12 Follow-up	3/12 Follow-up
Mean R.B.C. Count (m/cu. mm.)	4.12	4.87	4.66	4.49	5.05	5.02
Mean M.C.H.C. (per cent.)	28.3	31.6	31.5	30.9	31.3	31.8
Mean M.C.V. (cu)	77.3	88.4	90.3	85.6	86.2	85.9
Mean Plasma Iron (µg./100 ml.)	57	73	74	75	101	91



a further difference between Groups I and II. Thus, in the more anaemic individuals, the mean M.C.H.C. had risen by 11.3 per cent. of the initial value at 1 month, as compared with a rise of 1.3 per cent. in the remainder of the patients who were given S.O.I. The mean rise in R.B.C. in all the treated patients has already been commented upon, but it is apparent from Table V that this rise was slightly greater in Group I.

The mean M.C.V., which was below the normal range in Group I, was corrected by the 1 month follow-up.

Beyond the 1 month follow-up no material difference in the response of the two groups to S.O.I. was detected.

**E.S.R.**—In the patients treated with S.O.I., a marked fall in the E.S.R. occurred. At the start of the trial the mean level was 60 mm./hr, and 1 month after the end of the course of S.O.I. it was 29 mm./hr. By 3 months, however, the mean had risen to 37 mm./hr. Only one patient had an E.S.R. of less than 20 mm./hr initially, but the rate had fallen to this level in eleven cases at the 1 month follow-up. In contrast, the mean E.S.R. in the control group showed little change during the period of observation and the difference between the treated and control groups was significant ( $p < 0.01$ ).

**Plasma Iron Level.**—Whereas the mean plasma iron level in the control group showed a slight fall during the time of the trial, that in the treated group improved from 70  $\mu\text{g./100 ml.}$  initially to 93  $\mu\text{g./100 ml.}$  at one month, falling to 86  $\mu\text{g./100 ml.}$  at 3 months. Only four of the 26 patients in the treated group failed to show a higher level of plasma iron in the 3 months after receiving S.O.I. On the other hand, only four of the controls showed any improvement.

Comparison of the initial mean plasma iron levels in the eight more anaemic patients with the eighteen other patients in the treated group (Table V) reveals a lower level in the former, seven of whom were females. In six out of seven of these patients in whom marrow iron was estimated, iron was absent or present only in trace amounts.

**Rate of Clearance of S.O.I.**—In eleven patients in whom serial measurements of the clearance of 200 mg. S.O.I. were made, no change in the speed of clearance consequent on the administration of increasing amounts of iron was demonstrated. The mean rates of clearance from the plasma of a single injection of S.O.I. at the start of treatment, after 2 g. S.O.I. had been given, and at the end of the course, are shown in Table VI.

TABLE VI  
RATE OF CLEARANCE OF S.O.I. AFTER ADMINISTRATION  
OF INCREASING AMOUNTS IN ELEVEN PATIENTS

Amount of S.O.I. given before Estimation of Clearance (mg.)	Mean Plasma Iron Levels during Clearance ( $\mu\text{g./100 ml.}$ )			
	Before	12 hrs	18 hrs	24 hrs
200	88	265	179	119
2,200	96	180	129	106
5,000	139	194	155	142

**Functional Capacity.**—During the trial, improvement occurred in the grade of functional capacity in fifteen patients in the treated group, nine remained in the same grade, and two deteriorated. In the control group fourteen remained in the same grade throughout the trial and only six were placed in a higher grade at the 1 month or 3 month follow-up. The improvement which occurred in the treated group between the start of the trial and the 3 month follow-up was significant ( $p < 0.02$ ), whereas the change in the control group was not.

**Disease Activity.**—In fourteen patients in the treated group the disease became less active during the trial and in twelve there was no change. The improvement between the initial assessment and the 3 month follow-up in this group was significant ( $p < 0.01$ ). In the control group activity of the disease decreased in only three patients at the 1 month or 3 month follow-up, and in seventeen there was no change.

#### Factors Influencing Response to S.O.I.

**Age and Sex.**—The improvement in Hb levels tended to be greater in the older subjects than in the younger, but this was only a trend and did not reach levels of significance.

It was found that a greater rise in Hb level occurred in female patients in the treated group than in males (Table VII).

TABLE VII  
IMPROVEMENT IN HAEMOGLOBIN LEVEL IN TREATED  
AND CONTROL GROUPS BY SEX

Sex .. .. .	Group .. .. .	Male		Female	
		Treated	Control	Treated	Control
Mean Haemoglobin Increment (per cent.)	1 Month Follow-up	13.0	3.3	23.2	1.3
	3 Month Follow-up	12.7	6.7	21.2	3.2

The mean Hb level in males at the start of the trial was 75.5 per cent. and in females it was 71.4

per cent. Only in respect of the plasma iron concentration (males 85.1  $\mu$ g./100 ml., females 9.9  $\mu$ g./100 ml.) was there an appreciable difference between the initial findings in the two sexes.

**Hb Level, E.S.R., and Plasma Iron Concentration before Treatment.**—The increase in haemoglobin which occurred after the administration of S.O.I. was closely related to the initial degree of anaemia ( $r < 0.01$ ). Despite the fact that the Hb level was found to correlate with the activity of the disease, the initial E.S.R. showed no relationship to the subsequent improvement.

The degree of hypoferraemia at the start of the trial was not related to the response to S.O.I. Hence the better response of the females in the treated group compared with the males could not be attributed to their lower initial plasma iron concentration.

**Iron Content of Bone Marrow.**—The iron content of the bone marrow as estimated by the Prussian blue and chemical methods showed no relationship to the improvement in the Hb level or to the fall in E.S.R. which occurred after the administration of S.O.I. The lack of correlation between the improvement in haemoglobin level and the iron content of the marrow is shown in Table VIII. The nineteen patients tested by the Prussian blue method were divided into two groups depending on whether they were found to have reduced amounts of stainable iron in the marrow (nil or a trace) or easily detected amounts (+ or ++). In those with a reduced marrow iron content, the Hb improved from 73 per cent. initially to 92 per cent. at 1 month and 93 per cent. at 3 months. Those with normal or excessive amounts of stainable iron improved from 74 per cent. initially to 90 per cent. at 1 month and 91 per cent. at 3 months. The result was similar

when the fourteen patients, tested by the chemical method, were divided into two groups depending on whether the amount of iron was less or more than the mean level of 55 mg./100 g. protein.

#### Side-Effects of the Administration of S.O.I.

Despite the high doses of S.O.I. used in the trial, side-effects were notable by their absence. Only one patient complained of unpleasant symptoms in the form of flushing and back-ache after the first three to four injections.

#### Discussion

The results of this trial leave no doubt that the intravenous administration of saccharated oxide of iron leads both to improvement in anaemia and to diminution of disease activity in patients suffering from rheumatoid arthritis. A rise in the haemoglobin level of more than 14 per cent. (2 g. per 100 ml.), a figure adopted by Coleman, Stevens, and Finch (1955), and McCrea (1958) as constituting a significant response, occurred in sixteen of 26 patients during the period of observation. The mean increase in haemoglobin in the treated group exceeded 18 per cent. (2.7 g. per 100 ml.). By contrast, in the control group, the haemoglobin level improved by more than 14 per cent. in only two patients, the mean rise for the group being less than 5 per cent. (0.7 g. per 100 ml.).

The response to the administration of iron in simple iron deficiency anaemia is characterized by a proportionately greater rise in the M.C.H.C. than in the red cell count. In the majority of the treated group in this study only a slight increase in the M.C.H.C. took place, no greater than was observed in the controls. Only in those patients whose haemoglobin was below 70 per cent. before the administration of iron was a significant rise in M.C.H.C. and M.C.V. noted after one month, and their subsequent progress did not differ from the remainder of the treated group. It would appear that, in these eight patients of whom seven were females, a mild degree of iron deficiency was present, although no obvious cause was found.

Consideration of results in the treated group as a whole reveal other features which differentiate the response to S.O.I. in the anaemia of rheumatoid arthritis from that in simple iron deficiency. First, the increase in haemoglobin shows no relationship to the iron content of the bone marrow as estimated before the start of treatment. It has been reported by previous authors (Rath and Finch, 1948; Hutchison, 1953) that only those patients in whom

TABLE VIII

RELATIONSHIP BETWEEN IMPROVEMENT IN HAEMOGLOBIN LEVEL AND INITIAL IRON CONTENT OF BONE MARROW IN TREATED GROUP

Time of Assessment		Iron Content of Bone Marrow			
		Prussian Blue Method (19 cases)		Chemical Method (14 cases)	
		Nil and Trace	+ and ++	<55 mg./g. Protein	>55 mg./g. Protein
Hb (per cent.)	Start of Trial	73	74	77	77
	1 Month Follow-up	92	90	93	95
	3 Month Follow-up	93	91	92	96

iron cannot be demonstrated in the marrow by the Prussian blue technique will respond to the administration of iron. Although stainable iron was absent or present in reduced amounts in eleven of nineteen patients in the treated group, their response did not differ significantly from that of the remaining eight patients in whom it was demonstrated in normal or increased quantities.

Secondly, in iron deficiency anaemia there is maximal utilization of iron given in the form of S.O.I. by the intravenous route. The haemoglobin level rises by approximately 1 per cent. for each 25 mg. iron administered. No such dose-response could be demonstrated in this investigation. This may be related to the fact that, although absorption from the gut is normal in rheumatoid arthritis, the administration of iron by mouth is usually ineffective. These observations suggest that the dose of iron required to achieve a satisfactory response is much greater than the amount which would be required to correct anaemia due to simple iron deficiency and is probably very much in excess of the amount which can normally be absorbed from the alimentary tract.

Thirdly, improvement in the anaemia in the treated group was largely accounted for by the rise in the red cell count. This had increased by 13.5 per cent. of the initial count at the one month assessment and was well maintained after 3 months. Since there is no evidence that the administration of S.O.I. prolongs the life-span of red cells, the main effect on the blood picture of S.O.I. in the doses given must have been to increase, directly or indirectly, the capacity of the marrow to produce red cells.

In the anaemia of infection, which has been investigated in detail by Cartwright and Wintrobe (1955), hypoferraemia is a constant feature. It has been suggested that, in the presence of inflammation, iron is removed from the circulation by cells of the reticulo-endothelial system. The purpose of this uptake is unknown, but the possibility that saturation of the system with iron might be of benefit prompted the large doses used in this trial. Evidence for such saturation was sought by serial estimations of plasma iron and by the measurement of iron clearance at intervals throughout the course. Although a moderate rise in plasma iron took place, this bore no direct relationship to the rise in haemoglobin. In eleven patients in whom clearances were measured at intervals, the rate remained abnormally rapid. It would appear that, although the administration of 5 g. S.O.I. was followed by improvement in the blood picture in every case, even larger amounts may be required to restore plasma iron

to normal levels and to saturate the cells of the reticulo-endothelial system. Whether the administration of such larger quantities would achieve more satisfactory results without toxic effects cannot be predicted at present.

Perhaps the most remarkable change following the course of treatment was the striking fall in the mean E.S.R., accompanied by a significant improvement in functional capacity. That these changes cannot be attributed to the basic regimen of treatment used in all patients is authenticated by the significant difference between the treated group and controls. It would now appear justifiable to state with some confidence that in the majority of cases the beneficial effects of S.O.I. are due to a reduction in disease activity with concomitant improvement in the anaemia and not to the correction of iron deficiency at the level of the bone marrow.

Saccharated oxide of iron is rapidly removed from circulation by the phagocytic cells of the reticulo-endothelial system (Benacerraf, Biozzi, Halpern, and Stiffel, 1957). The same authors have shown experimentally that repeated injections of S.O.I. and other colloids have a powerful stimulating effect on the reticulo-endothelial system in animals. They state that the mechanism of this action is unknown, but the evidence suggests that it is due to an increase in the number of phagocytic cells. They have also shown that the reticulo-endothelial system resists remarkably all attempts to blockade its phagocytic activity by the injection of colloidal particles (Biozzi, Halpern, Benacerraf, and Stiffel, 1957). This observation is in keeping with the failure of 5 g. S.O.I. to alter the abnormally rapid clearance of a single dose of 200 mg. in these patients.

What bearing these facts may have on the therapeutic effect of large doses of S.O.I. in rheumatoid arthritis is quite unknown at present. The possibility exists that the observed effects of S.O.I. may not depend on its iron content and that similar results might follow the use of other colloids.

The authors do not recommend the routine use of such large doses of S.O.I. in the treatment of rheumatoid arthritis, but the results of this controlled trial would certainly indicate the need for a more detailed investigation of the metabolism of this compound, with particular reference to its possible effects on the function of the reticulo-endothelial system.

### Summary

(1) The effects of the intravenous administration of 5 g. saccharated oxide of iron were studied in a group of 26 patients suffering from rheumatoid



arthritis. Their progress was compared with that of twenty patients who received the same basic regimen of treatment, but to whom no iron was given.

(2) The treated group showed a significantly greater improvement in the anaemia than the control group.

(3) The rise in the haemoglobin level in the treated group was associated with a fall in the mean level of the erythrocyte sedimentation rate. Functional capacity improved and disease activity diminished simultaneously.

(4) The rise in the haemoglobin level resulting from the administration of saccharated oxide of iron was not related to the initial iron content of the marrow, the degree of anaemia, the mean corpuscular haemoglobin concentration, the plasma iron level, or the activity of the disease.

(5) Improvement in anaemia in the treated patients was due mainly to a rise in the red cell count and not to correction of hypochromia.

(6) The significance of these findings is discussed.

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#### Nature de l'anémie dans l'arthrite rhumatismale IV. Effets de l'administration intraveineuse d'oxyde saccharé de fer

## RÉSUMÉ

(1) Les effets de l'administration intraveineuse de 5 g. d'oxyde saccharé de fer furent étudiés chez un groupe de 26 malades atteints d'arthrite rhumatismale. Leur progrès fut comparé à celui de 20 malades soumis à un régime de traitement similaire, mais sans la thérapie au fer.

(2) Le groupe traité accusa une amélioration de l'anémie appréciablement plus accentuée que le groupe témoin.

(3) L'augmentation du taux d'hémoglobine chez le groupe traité fut accompagnée d'une chute de la vitesse moyenne de la sédimentation érythrocytaire. La capacité fonctionnelle s'améliora et l'activité morbide diminua en même temps.

(4) L'augmentation du taux d'hémoglobine due à l'administration d'oxyde saccharé de fer ne fut pas en relation avec le taux initial de fer dans la moelle, la sévérité de l'anémie, la concentration corpusculaire d'hémoglobine, le taux plasmatique de fer ni l'activité morbide.

(5) L'amélioration de l'anémie des malades traités était due surtout au nombre augmenté d'érythrocytes et non pas à l'hypochromie corrigée.

(6) On discute la portée de ces résultats.

#### La naturaleza de la anemia en la artritis reumatoide. IV. Efectos de la administración endovenosa de óxido sacarado de hierro

## SUMARIO

(1) Se estudiaron los efectos de la administración endovenosa de 5 g. de óxido sacarado de hierro en un grupo de 26 enfermos con artritis reumatoide. Su progreso fué comparado al de 20 enfermos sometidos a un régimen básico similar, pero sin tratamiento férrico.

(2) El grupo tratado acusó una mejoría de la anemia significativamente mayor que el grupo testigo.

(3) El aumento de la tasa de hemoglobina en el grupo tratado se vió asociado a una caída del promedio de la velocidad de eritrosedimentación. La capacidad funcional mejoró y la actividad morbosa disminuyó al mismo tiempo.

(4) El aumento de la cifra de hemoglobina debido a la administración de óxido sacarado de hierro no se relacionaba con la tasa inicial del hierro medular, la severidad de la enfermedad, la concentración corpuscular de hemoglobina, la tasa plasmática de hierro ni la actividad morbosa.

(5) La mejoría de la anemia de los enfermos tratados se debió ante todo al aumento de la cifra eritrocitaria y no a la corrección de la hipocromia.

(6) Se discute el alcance de estos resultados.

See Appendix containing principal clinical and laboratory data on patients studied, on pp. 414 and 415 (overleaf).



Group	Sex	Age	Duration of Symptoms (yrs)	Initial Iron Content of Bone Marrow		Haemoglobin (per cent.)			Red Cell Count (millions/cu. mm.)		
				Prussian Blue Method	Chemical Method (mg./g. protein)	Initial	1 mth	3 mth	Initial	1 mth	3 mth
Treated (26)	*M	70	10	—	—	45	96	83	3.54	4.84	4.52
	*F	39	1	—	—	48	94	87	3.31	4.83	4.42
	*F	60	8/12	++	89	60	80	96	4.75	4.82	4.79
	*F	73	9	—	21	60	97	77	3.95	5.14	3.96
	*F	53	10	—	—	63	78	74	4.26	4.75	4.38
	*F	62	7	Trace	—	69	106	99	4.66	5.13	5.02
	*F	52	6	Trace	—	69	87	94	4.13	4.67	4.63
	*F	49	12	Trace	—	70	97	110	4.32	4.75	5.52
	M	44	4	—	—	71	82	89	4.72	4.95	4.92
	F	65	16	+	—	73	84	80	4.41	5.15	4.78
	F	70	3	+	—	74	104	105	4.35	5.64	5.26
	F	52	4	—	88	75	83	86	4.48	4.97	4.88
	F	65	24	—	—	75	101	101	4.01	5.21	5.13
	F	56	15	—	—	76	84	86	4.85	5.18	4.94
	F	55	7	—	35	77	97	99	4.43	4.91	4.93
	F	45	2	+	—	78	84	84	4.62	4.82	4.86
	F	67	3	+	49	78	88	98	4.46	4.81	5.45
	F	65	6/12	+	28	79	99	108	4.52	5.01	6.07
	F	52	8	—	76	80	84	87	4.00	4.20	4.43
	M	58	3	+	55	80	84	78	4.82	4.86	4.78
	M	59	6	+	38	80	86	88	4.88	5.38	4.94
	F	18	4	—	32	82	90	80	4.25	4.66	4.31
	M	54	20	++	92	82	106	104	4.87	4.99	5.06
	M	66	6	Trace	31	83	86	93	4.74	6.01	5.35
	F	62	6/12	Trace	109	85	110	107	4.23	5.27	5.34
	M	55	16	—	29	88	97	94	4.32	4.81	4.94
Mean Values and Standard Deviations						73.1 ±10.2	91.9 ±6.9	91.8 ±10.2	4.37 ±0.49	4.96 ±0.54	4.92 ±0.44
Control (20)	*F	29	18/12	—	27	65	76	76	4.25	4.78	4.82
	F	56	10	—	—	72	89	83	4.62	4.94	5.08
	M	49	2	+	51	74	90	84	4.82	5.17	4.96
	F	49	6	+	41	76	76	77	4.72	4.80	4.80
	M	64	14	Trace	—	78	70	79	4.86	4.15	4.79
	F	55	30	Trace	57	78	70	79	4.86	4.85	4.79
	F	65	10	—	—	78	82	84	4.80	4.62	4.92
	F	52	11	Trace	—	78	76	72	4.85	4.64	4.35
	F	52	17	+	—	78	88	87	4.84	4.96	4.80
	M	48	4	Trace	12	79	86	94	4.82	5.01	5.08
	F	59	8	—	67	80	73	77	4.79	4.43	4.23
	M	32	3	—	—	80	84	90	5.22	5.29	4.83
	F	52	5	+	54	80	79	80	4.75	4.60	4.34
	M	54	12	—	—	82	88	88	4.71	4.92	4.97
	M	57	22	+	13	82	87	95	5.01	5.34	5.64
	F	67	3	—	52	83	87	92	4.68	4.90	4.83
	F	44	6	+	59	84	84	88	5.88	5.08	5.00
	F	62	4/12	—	—	84	80	88	5.12	5.10	5.01
	F	71	12	—	49	85	84	83	4.43	4.44	4.38
	M	62	6	+	33	86	79	32	4.27	4.26	4.50
Mean Values and Standard Deviations						79.1 ±4.8	82.0 ±6.1	83.9 ±6.2	4.75 ±0.23	4.81 ±0.33	4.81 ±0.34

\* Patients with initial Hb of 70 per cent. or lower.

APPENDIX

DATA OF PATIENTS STUDIED IN THE TRIAL

3 mth	Mean Corpuscular Haemoglobin Concentration (per cent.)			Plasma Iron ( $\mu\text{g./100 ml.}$ )			Erythrocyte Sedimentation Rate (mm./hr)			Grade of Functional Capacity			Grade of Disease Activity		
	Initial	1 mth	3 mth	Initial	1 mth	3 mth	Initial	1 mth	3 mth	Initial	1 mth	3 mth	Initial	1 mth	3 mth
4-52	26.4	31.6	31.8	53	53	58	118	44	66	IV	II	II	3	2	2
4-42	27.3	30.2	30.7	28	50	80	72	25	43	II	I	I	3	2	2
4-79	24.0	30.5	31.6	68	80	94	60	29	39	II	II	II	2	2	2
3-96	29.7	31.2	31.6	44	44	54	65	20	67	IV	II	II	3	1	2
4-38	28.2	29.4	31.2	35	131	66	85	82	43	II	II	II	3	2	2
5-02	29.8	34.1	33.5	74	79	63	30	22	23	II	II	II	2	2	2
4-63	30.0	31.4	30.9	63	69	74	36	19	16	III	III	III	2	2	2
5-52	31.2	34.3	30.8	95		104	58	8	3	IV	III	II	2	2	2
4-92	28.2	29.3	31.4	67	81	58	108	19	38	III	II	II	3	2	2
4-78	27.8	29.8	29.8	120	158	94	20	8	9	III	III	IV	2	2	1
5-26	31.2	32.1	33.0	52	77	85	72	17	34	III	III	III	2	2	2
4-88	29.2	30.2	31.8	70	123	75	95	8	26	III	II	II	3	1	2
5-13	31.8	31.2	35.7	42	89	98	44	19	18	III	II	III	2	2	2
4-94	28.6	28.4	29.5	123		99	42	21	13	III	II	I	3	2	1
4-93	30.8	31.3	32.6	51	132	79	49	39	62	III	III	III	2	2	2
4-86	28.4	29.8	30.5	125	123	118	86	50	82	II	I	I	3	2	2
5-45	32.9	34.5	30.9	31	59	83	70	44	29	III	II	I	2	2	2
6-07	32.6	32.2	31.4	24	28	109	60	14	8	III	III	IV	3	2	2
4-43	30.5	31.3	32.2	76	51	48	88	72	88	III	III	III	3	3	2
4-78	32.3	30.5	28.0	68	69	127	76	37	60	II	II	II	2	2	2
4-94	29.0	28.8	31.2	76	169		26	12	8	III	II	II	2	1	1
4-31	33.9	34.1	34.0	86	170	118	60	46	57	III	III	II	2	2	2
5-06	27.4	32.5	33.5	130	104	100	9	7	29	II	I	I	2	1	2
5-35	31.8	30.1	31.6	87	115	114	28	19	13	II	II	II	2	2	2
5-34	34.1	35.6	35.5	70	113	82	41	40	42	III	II	II	2	2	2
4-94	32.0	32.0	29.2	54	60	66	64	42	47	IV	III	III	3	2	2
4-92	30.4	31.4	32.0	70	93	86	60	29	37						
$\pm 0.44$	$\pm 0.6$	$\pm 1.8$	$\pm 2.7$	$\pm 29$	$\pm 38$	$\pm 21$	$\pm 27$	$\pm 19$	$\pm 23$						
4-82	27.4	28.2	28.2	63		42	56	42	7	III	II	II	3	2	1
5-08	32.7	33.8	30.8	78	58	19	36	14	21	III	II	II	2	2	2
4-96	27.3	31.6	32.9	100	62	87	41	15	69	II	II	II	2	2	2
4-80	28.2	27.2	27.2	116		69	72	60	43	II	II	II	2	2	2
4-79	29.5	32.6	32.0	100	79	47	54	36	41	II	II	II	2	2	2
4-79	28.0	25.4	31.0	88	45	53	25	48	41	III	III	III	2	2	2
4-92	30.3	29.3	29.8	58	59	59	37	70	52	II	II	II	2	2	2
4-35	31.5		33.5	49	32	15	15	13		III	III	III	2	2	2
4-80	28.0	31.0	33.9	35	49	75	92	91	93	IV	III	III	2	2	2
5-08	31.6	31.8	33.1	94	66	62	28	40	35	II	II	II	2	2	2
4-23	31.4	29.2	32.6	135	67	77	44	68		III	II	II	2	2	2
4-83	27.7	28.2	31.7	109	83	90	30	29	24	II	II	II	2	2	2
4-34	29.0	30.0	33.0	66	70	54	30	39	55	III	III	III	2	2	2
4-97	30.8	30.9	31.0	119	89	96	56	69	73	III	III	III	2	2	2
5-64	31.6	30.8	34.4	82	63	74	47	21	25	II	II	II	2	2	2
4-83	33.5	31.4	33.6	42	85	56	43	43	52	II	II	II	2	2	2
5-00	29.8	29.8	30.4	100	52	70	54	21	40	III	III	III	2	2	2
5-01	29.1	29.8	31.2	62	35	39	30	84	81	III	III	II	2	2	2
4-38	30.8	31.2	33.1	49	44	39	71	80	96	IV	III	III	3	2	3
4-50	33.5	31.6	32.4	65	68	61	94	100	45	II	II	II	3	2	1
4-81	30.1	30.4	31.8	80	63	60	50	49	46						
$\pm 0.34$	$\pm 1.7$	$\pm 1.2$	$\pm 0.9$	$\pm 28$	$\pm 16$	$\pm 20$	$\pm 15$	$\pm 27$	$\pm 21$						

## THE DERMAL BARRIER IN SYSTEMIC SCLEROSIS AND OTHER RHEUMATIC DISEASES

BY

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Hyaluronidase has been shown to increase the rate of spread of intradermally injected solutions in animals (Chain and Duthie, 1939, 1940) and the whole subject of spreading factors was reviewed by Duran-Reynals (1942). Holborow and Keech (1951) studied the effects of hyaluronidase in accelerating the rate of spread of a solution of haemoglobin injected intradermally in normal human subjects and in patients with rheumatic fever and found no significant differences. In three cases of dermatomyositis, the hyaluronidase appeared to have no significant spreading effect until hypersensitivity to the enzyme developed, and the authors suggested that, in dermatomyositis, the hyaluronic component of the skin is either deficient or is unresponsive to testicular hyaluronidase.

Kellgren, Ball, and Tutton (1952) compared the rates of disappearance of the palpable blebs produced by the intradermal injection of isotonic saline with and without hyaluronidase in normal and acromegalic subjects, and found that, whereas the rates of disappearance of the saline blebs were comparable in the two groups, the hyaluronidase caused more rapid disappearance of the blebs in the normal than in the acromegalic subjects. In normal subjects, the blebs containing hyaluronidase tended to persist longer in the younger subjects who might still be growing.

The purpose of this communication is to report the results obtained on applying this test in normal subjects and in patients suffering from systemic sclerosis or other connective tissue diseases. Some of the factors concerned in the disappearance of the blebs were investigated and the possible significance of the results is discussed.

### Methods

The test procedure was that described by Kellgren and others (1952). Eight sites for injection were chosen on the volar aspect of the forearm in two rows, there being

2 in. between the rows and at least 1 in. between the sites in each row. At each of four sites 0.05 ml. physiological saline, and at the other four sites 0.05 ml. saline containing freshly added hyaluronidase, was injected intradermally. Two injections of saline and two of saline containing hyaluronidase were made at alternate sites in each row. The time taken for the intradermal blebs to become impalpable was then recorded.

The saline injections were made first, the time required to raise the four blebs varying from 30 seconds to 2 minutes. The injections of saline containing hyaluronidase were then made, each bleb being followed to disappearance before the next injection was made.

Testicular hyaluronidase (Benger's "Hyalase") was used in a concentration of 1,500 i.u. in 100 ml. physiological saline, almost all the experiments being performed with either Batch 11065 or Batch 14355. The activity of the enzyme solution was tested before each experiment by intradermal injection in a normal subject, usually one of the authors, neither of whom developed hypersensitivity to the enzyme.

Skin temperatures were measured by a thermocouple applied to the skin surface.

In the experiments employing radioactive sodium,  $^{24}\text{Na}$ , the isotonic saline solutions with and without hyaluronidase were made up so that the 0.05 ml. injected contained 2 to 5 microcuries of  $^{24}\text{Na}$ . Care was taken when making the injections to avoid contamination of the skin surface.

Gamma radiation was counted using a crystal scintillation counter connected to a rate-meter, the counting rate being recorded every 15 sec., starting after removal of the syringe, until a background level had been reached. These values, less the background value, were plotted semi-logarithmically against time. The average dimension of the blebs was  $7 \times 8$  mm., and the radiation was counted from the blebs and surrounding area through a circular lead-screened opening 12 mm. in diameter, or from the centre of the blebs through an opening 4 mm. in diameter, as indicated in the text.

The sheep cell agglutination tests were performed by the method of Ball (1950); agglutination at a titre of 1/32 or higher after 18 hrs' incubation was recorded as a positive result.

The full test, as described, was performed on one normal male subject aged 28, on 4 different days. The mean durations of the hyaluronidase blebs ranged from 2.25 to 4.9 minutes (average 4.5), and those of the saline blebs from 55 to 67 minutes (average 62.2). This suggested that the results were reasonably reproducible.

The question of observer difference in assessing the duration of the blebs was investigated in three normal subjects and in one patient with systemic sclerosis, the duration of the blebs being assessed independently by each of the authors (Table I). Satisfactory agreement in the average time of disappearance of each type of bleb was obtained.

### Results

The test was performed on nineteen normal subjects ranging in age from 17 to 68 years (average 39), of whom five were males. The results are shown in Table II. The average duration of the saline blebs was 61.7 minutes and of the hyaluronidase blebs 3.9 minutes. Kellgren and others (1952)

obtained average durations of 36 and 2.2 minutes respectively for the two kinds of blebs, using this test in normal subjects whose average age was 35 years (range 16 to 69). Since the average duration of each kind of bleb in our experiments was increased in approximately the same proportion above these figures, it would appear that the difference was probably due to observer difference in assessing the time of disappearance of blebs.

Nineteen patients with systemic sclerosis of whom two were males were tested. Their ages ranged from 11 to 78 years and were distributed similarly to those of the normal subjects. The sheep cell agglutination test was positive in six of the eighteen patients tested. All of them had sclerosis of the skin with loss of mobility over underlying structures; the skin was normal at the site of testing on the forearm in only one patient, who is more fully described later. Considering the eighteen patients in whom the forearm skin was abnormal, the mean

TABLE I  
INTER-OBSERVER DIFFERENCE IN HYALURONIDASE AND SALINE BLEB DISAPPEARANCE TIMES

Subject	Age (yrs)	Sex	Duration of Blebs (min.)							
			Hyaluronidase				Saline			
			Observer 1		Observer 2		Observer 1		Observer 2	
			Mean	Range	Mean	Range	Mean	Range	Mean	Range
Normal ..	19	M	5.2	4.0-5.75	4.9	4.0-5.25	80	54-109	87	84-89
Normal ..	25	F	4.3	3.0-5.0	4.1	3.0-5.0	71	48-79	69.5	55-80
Normal ..	18	F	4.6	2.0-5.5	4.1	1.5-5.5	—	—	—	—
Sclerotic ..	22	F	9.25	7-12.5	8.6	6.5-11.5	—	—	—	—

TABLE II  
DURATION OF SALINE BLEBS WITH AND WITHOUT HYALURONIDASE IN NORMAL SUBJECTS AND PATIENTS WITH RHEUMATIC DISEASES

Diagnosis	Number of Subjects			Age (yrs)		Duration of Blebs (min.)							
						Hyaluronidase				Saline			
						Mean			Range	Mean			Range
						Value	S.D.	Significance of difference from normal <i>P</i>		Value	S.D.	Significance of difference from normal <i>P</i>	
Normal ..	5	14	19	39	17-68	3.9	0.8	—	2.8-5.3	61.7	16.7	—	34.8-92
Systemic Sclerosis ..	2	17	19	45	11-78	6.6	5.3	<0.05	1.1-23.5	22.6	13.9	<0.001	3.8-51.5
Dermatomyositis ..	1	1	2	59	57-61	3.7			2.8-4.6	40.4			7.8-73
Rheumatoid Arthritis ..	5	4	9	40	26-62	3.6	0.7	~0.40	2.6-5.8	50.5	20.4	~0.15	17.5-84
Ankylosing Spondylitis	23	0	23	52	27-65	3.3	1.1	<0.05	1.2-5.8	—	—	—	—
Miscellaneous Connective Tissue Disorders	4	12	16	45	25-64	3.5	2.0	>0.9	<1.0-9.1	35.0	12.7	<0.001	<4.0-57.9



duration of the blebs containing hyaluronidase (6.6 minutes) was longer and that of the saline blebs (22.6 minutes) was shorter than in normal subjects ( $p < 0.05$  and  $< 0.001$  respectively) (Table II). Only three of these patients were receiving steroid or corticotrophin therapy. In two of these the duration of the hyaluronidase blebs was normal and in the third it was shorter than normal, so that a decrease in the effect of the hyaluronidase due to these agents (Seifter, Baeder, and Dervinis, 1949; Shuman and Finestone, 1950) could not explain the results.

The results of the tests in the nineteen individual patients with systemic sclerosis and in the nineteen normal subjects are indicated in Fig. 1. In normal subjects the duration of the blebs fell within the two standard deviations above and below the mean normal values for both saline and saline plus hyaluronidase.

The probability that the duration of either type of bleb would fall outside these limits by chance would be  $1/20$ , and the probability that both would do so is considerably less. Only one patient with systemic sclerosis came within this range. She had noted deterioration in her general health, stiffness in the limbs, and attacks of Raynaud's phenomenon for 2 years, and had more recently developed a sclerodermatous plaque on the forehead. Motion of many of her joints was limited and accompanied by fine "squeaking" crepitus which was also present on

movement of tendons. There were possible early sclerotic changes in the skin of the feet, but the skin of the upper limbs was normal. In ten of the remaining eighteen patients with systemic sclerosis, the skin at the site of testing, though sclerotic, was of normal or increased thickness, but in the remainder who had more advanced changes the skin was thinner than normal and more tightly bound. The results in these two groups of patients are given in Table III (opposite). The average duration of saline blebs in patients with less advanced skin changes (23 minutes) was almost identical with that in those with advanced changes (22.1 minutes), but the hyaluronidase was relatively less effective in accelerating the disappearance of blebs in those with earlier changes, the average duration of the blebs being 8.6 minutes in this group compared with 5.2 minutes in those with advanced changes ( $p < 0.20$ ). The advanced skin changes were of course usually encountered in patients with longer duration of symptoms. Fourteen patients (average age 42 years) had had symptoms for 5 years or less, and five (average age 33 years) for more than 5 years (average 12.4). The mean duration of the hyaluronidase blebs in these two groups was 7.5 and 4.1 minutes respectively ( $p \sim 0.25$ ), and that of the saline blebs 24.9 and 16.1 minutes ( $p \sim 0.25$ ).

The two patients listed in Table II under the diagnosis of dermatomyositis were both suffering from the classical acute form of the disease.

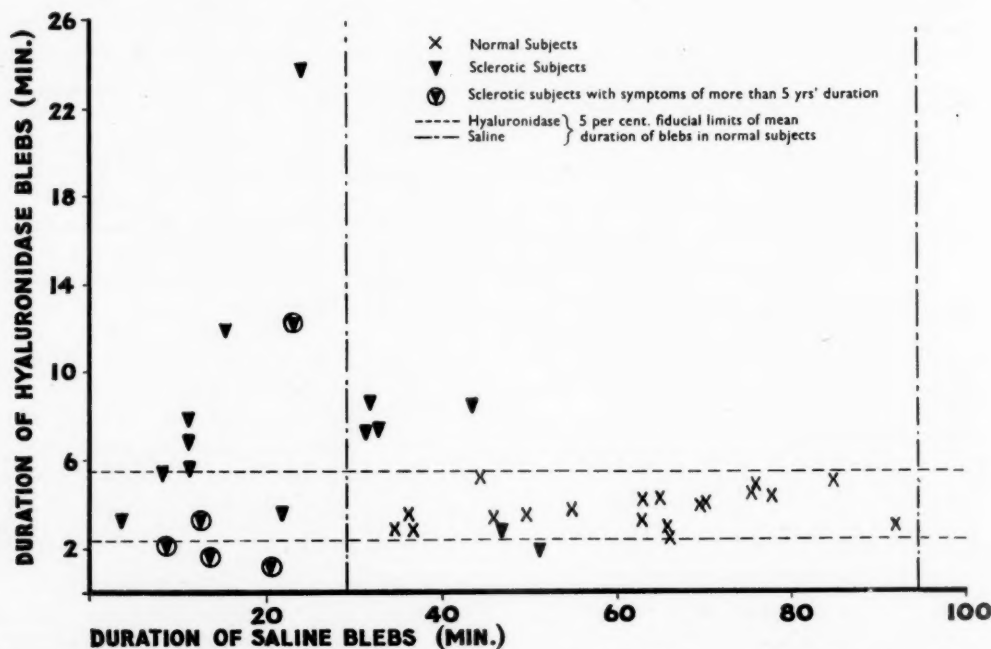


Fig. 1.—Duration of saline and hyaluronidase blebs in nineteen normal subjects and in nineteen patients with systemic sclerosis.

TABLE III

DURATION OF BLEBS IN PATIENTS WITH SYSTEMIC SCLEROSIS WITH EARLY AND LATE SKIN CHANGES

State of Skin	No. of Patients			Age Range (yrs)	Duration of Blebs (min.)			
					Saline		Hyaluronidase	
	Male	Female	Total		Range	Mean	Range	Mean
Sclerotic but of normal or increased thickness	1	9	10	11-78	3.8-51.5	23	3.3-23.8	8.6
Tight and more tightly bound	1	7	8	14-62	9.4-43.6	22.1	1.1-8.5	5.2

## Case Reports

**Case 1, a housewife aged 61 years,** had had dysphagia for 6 months and progressive muscle weakness and rash for 2 months. There was an initial improvement on prednisone therapy, but she died 6 weeks after admission to hospital. At autopsy there were widespread metastases of an adenocarcinoma of uncertain origin (? ovary). The trunk and proximal limb muscles were wasted and their cut surfaces were of a pale orange colour; histologically there were focal degenerative changes in which the sarcoplasm had largely or completely disappeared and there was marked proliferation of sarcolemma cells, but there was no widespread loss of cross-striation or acute inflammatory process.

The test was performed before steroid therapy was started when the forearm was slightly oedematous. The mean duration of the hyaluronidase blebs was 2.8 minutes and that of the saline blebs 7.8 minutes.

**Case 2, a man aged 57,** gave a 4 months' history of rash, facial oedema, and muscle weakness and wasting; the "constant length phenomenon" could be demonstrated in many muscle groups. Electromyography revealed changes typical of myositis, and the urinary excretion of creatine was greatly increased.

The patient was receiving 15 mg. prednisolone daily at the time of the test. The skin of the forearm was warm, erythematous, and slightly scaly, thickened, indurated, and oedematous. The mean duration of the hyaluronidase blebs was 4.6 minutes and that of the saline blebs 73 minutes.

Nine patients aged from 26 to 42 years who satisfied the criteria of the American Rheumatism Association for a diagnosis of "definite" rheumatoid arthritis (Ropes, Bennett, Cobb, Jacox, and Jessar, 1956) were tested; five of them were males. The sheep cell agglutination test was performed on eight of them and was positive in five. The mobility of the skin was normal in all except one man aged 43 with familial anhidrosis, who had had rheumatoid arthritis for 6 years. The skin of his hands was dry, shiny, and atrophic, and there was some loss of skin mobility over the middle and distal phalanges and to a lesser degree over the left forearm where the test was performed. In this patient the mean duration of the saline blebs was 17.5 minutes and that of the

hyaluronidase blebs 3.2 minutes, but in the group of rheumatoid patients as a whole the average durations (50.5 and 3.6 minutes respectively) did not differ significantly from those in the normal subjects.

23 male patients with "typical" ankylosing spondylitis (Sharp, 1957) ranging in age from 27 to 65 years (average 52) were studied. The sheep cell agglutination test was performed on sixteen of them and was negative in all. Only blebs containing hyaluronidase were investigated and their average duration (3.3 minutes) was shorter than normal ( $p < 0.05$ ), a finding which may repay further investigation. West (1949) suggested that the symptom of "stiffness", which is usually a striking feature of the active stages of ankylosing spondylitis, may be due to a disturbance of the lubricant properties of the connective tissue ground substance, and that a defect of the metabolism of hyaluronic acid or related substances in the ground substance may play a part in the aetiology of the disease.

The group of patients with miscellaneous connective tissue diseases was composed as follows:

One had definite and another suspected disseminated lupus erythematosus.

One was suffering from hypopituitarism associated with rheumatoid arthritis.

One had Dupuytren's contractures and generalized thinness of the skin, but no evidence of hypopituitarism.

One had rheumatoid arthritis and scleroedema of the upper limbs.

Three had severe attacks of Raynaud's phenomenon with evidence of occlusion of digital arteries in two cases.

One, who had a polyarthritis with a subcutaneous elbow nodule and a positive sheep cell agglutination test, had severe Raynaud's attacks in the fingers with a normal reactive hyperaemia but with atrophy and sclerosis of the skin of the fingers and some loss of mobility of the skin of the distal forearms and face, but no rash. Muscle weakness had been a feature of relapses of the disease and the forearm muscles were firmer than normal and a "constant length phenomenon" could be demonstrated.

One, who had a polyarthritis and a positive sheep cell test, had, in the earlier stages of the illness, had a rash on the trunk, extremities, and eyelids associated with profound muscle weakness. The rash and weakness subsided as the process remitted, but there was mild residual contracture in limb muscles. This phase of the illness closely resembled acute dermatomyositis but, during a subsequent relapse, the patient developed florid psoriasis with nail changes and absorption of the terminal phalanx of one finger and the rash and arthritis eventually passed into simultaneous remission.

In all these patients the rates of disappearance of the blebs did not differ significantly from normal.

Two patients had widespread connective tissue changes associated with visceral lesions and generalized oedema, but no definite diagnosis could be made.

One patient was suffering from hypopituitarism, rheumatic heart disease, and severe Dupuytren's contractures.

In these three the duration of the blebs both with and without hyaluronidase was shorter than normal.

One patient had rheumatoid arthritis with visceral lesions which had been preceded by severe myositis.

In this case the blebs containing hyaluronidase disappeared more rapidly than normal, but the duration of the saline blebs was normal.

Abnormal persistence of the hyaluronidase blebs was noted in two patients: one was an acromegalic and the other had severe Raynaud's attacks with atrophy and sclerosis of the skin of the digits and distal forearms without visceral involvement. The latter was thought to be suffering from a primary arteritis with secondary changes in the skin, but systemic sclerosis could not be excluded.

#### Investigation of Factors concerned in the Disappearance of Blebs

(a) **Volume of Injection.**—In systemic sclerosis there is usually increased resistance to the intradermal injection of fluid and increased extrusion of fluid along the needle track so that the abnormal duration of the blebs might be due to a diminished residual volume of injected solution. To investigate this possibility the test was performed using different volumes of injection in a normal subject and in two patients with well marked scleroderma, all at comparable skin temperatures (see (b) below). The results (Table IV) suggest that a diminished amount of fluid remaining at the injection site was unlikely to be a major cause of the prolonged duration of the

blebs containing hyaluronidase observed in sclerodermatous patients. From animal experiment, Hechter (1947) concluded that, within wide limits, the volume of hyaluronidase solution injected intradermally had little influence on the time taken for the bleb to flatten out.

TABLE IV  
EFFECT OF VOLUME OF INJECTION

Subject	Volume (ml.)	Duration of Blebs (min.)		Skin Temperature (° C.)
		Hyaluronidase	Saline	
Normal	0.03	4.3	77.3	32.3
	0.05	4.3	65.8	32.2
	0.10	3.5	73.2	32.2
Systemic Sclerosis	1	0.03	5.4	31.8
		0.05	6.1	30.4
		0.10	7.3	31.4
	2	0.03	9.4	33.1
		0.05	7.5	32.4

(b) **Skin Temperature and Blood Flow.**—Thickening of the intima of medium-sized and small arteries resulting in diffuse narrowing and occlusion of the lumen is a characteristic feature of the pathology of systemic sclerosis (Lewis, 1940; O'Leary, Montgomery, and Ragsdale, 1957; Rodnan, Schreiner, and Black, 1957), so that it appeared possible that the longer duration of the hyaluronidase blebs in this condition might be the result of a reduction in the skin temperature from diminished blood flow through the skin.

To investigate this possibility, the test was performed in three normal subjects at high and low skin temperatures induced by whole body heating and cooling. In two of them the test was performed at high and low skin temperatures both with the circulation intact and with the arterial circulation occluded by a cuff applied proximally to the limb. The results are shown in Table V (opposite). Occlusion of the arterial circulation appeared to have little effect on the rates of disappearance of the blebs but changes in skin temperature resulted in large alterations in the disappearance rates irrespective of the presence or absence of a free circulation, the rates being considerably showed by reduction in the skin temperature. The skin temperature had not been recorded in most of the patients with systemic sclerosis, but the available observations (Table VI, opposite) suggested that it was unlikely that the longer duration of the hyaluronidase blebs was due

TABLE V  
EFFECT OF SKIN TEMPERATURE AND CIRCULATION IN THREE NORMAL SUBJECTS

Subject No.	Skin Temperature (°C.)		Mean Duration of Blebs (min.)				
	Range during Test	Mean	Circulation Intact		Circulation Occluded		
			Hyaluronidase	Saline	Hyaluronidase	Saline	Duration of Occlusion (min.)*
1	21.2-23.4	22.3	7.7	74.1			
	23.0-25.5	24.3			7.9	91	$\frac{20}{21.5} \rightarrow \text{off } 2$
	32.3-32.8	32.6	1.5	47.3			
	33.5-34.6	34.1			2.3	40.5	$\frac{20}{19} \rightarrow \text{off } 2$
2	27.8-24.4	26.1	5.8	42			
	33.1-34.4	33.8	2.9	29.3			
3	22.0-23.5	22.8	6.0	79.5			
	23.0-22.8	22.9			6.2	68.3	15
	21.5-25.4	23.5			4.0	49.5	$\frac{20.5}{17} \rightarrow \text{off } 2$
	34.0-33.0	33.5	1.0	27.0			
	33.5-32.0	32.8			2.5	36.5	$\frac{21}{13} \rightarrow \text{off } 2$
	33.5-32.3	32.9			1.1	29.0	18

\* The circulation was occluded just before the injections were made and the blebs containing hyaluronidase were followed to disappearance during the period of occlusion.

TABLE VI  
DURATION OF BLEBS IN SIX PATIENTS WITH SYSTEMIC SCLEROSIS IN WHOM SKIN TEMPERATURE WAS RECORDED

Patient No.	Age (yrs)	Duration of Symptoms (yrs)	Skin Temperature (°C.)	Duration of Blebs (min.)	
				Hyaluronidase	Saline
1	14	1.7	34.0	3.5	21.9
2	17	9.0	30.3	6.6	37.0
3	17	3.0	30.0	8.6	31.8
4	21	2.5	30.4	6.1	35.4
5	37	3.3	32.4	7.5	24.2
6	47	5.0	30.5	8.5	43.6

to a reduced skin temperature in the sclerodermatous patients.

(c) **Clearance of Radioactive Sodium.**—The results of an experiment in a normal subject in which the injections contained radioactive sodium are shown in Fig. 2 (overleaf). The rate of disappearance of the radioactive sodium from the injection site and its immediate vicinity was slightly increased by the hyaluronidase, the half-clearance time of the radioactive sodium being 7.1 minutes without and 5.6

minutes with hyaluronidase. Repetition of this experiment in the same subject on a different occasion gave half-clearance times of 5.8 and 5.1 minutes respectively. When the disappearance of radioactive sodium from the centres of the blebs was investigated in this subject by counting the radiation through a circular aperture 4 mm. in diameter placed over the centre of the bleb, the half-clearance times were 4.5 minutes without and 3.5 minutes with hyaluronidase. Thus, in each case, the rate of disappearance of the radioactive sodium was slightly accelerated by the hyaluronidase, but in this respect its effect was much less than its effect in increasing the rate of disappearance of the palpable bleb. Barron, Veall, and Arnott (1951) could find no correlation between the rate of clearance of radioactive sodium after intradermal saline injections in tubed skin pedicles and the persistence time of the blebs. Occlusion of the arterial circulation (Fig. 3, overleaf) caused cessation of sodium clearance from the centre of the bleb in the case of saline injections, and there was barely detectable clearance from the bleb containing hyaluronidase.



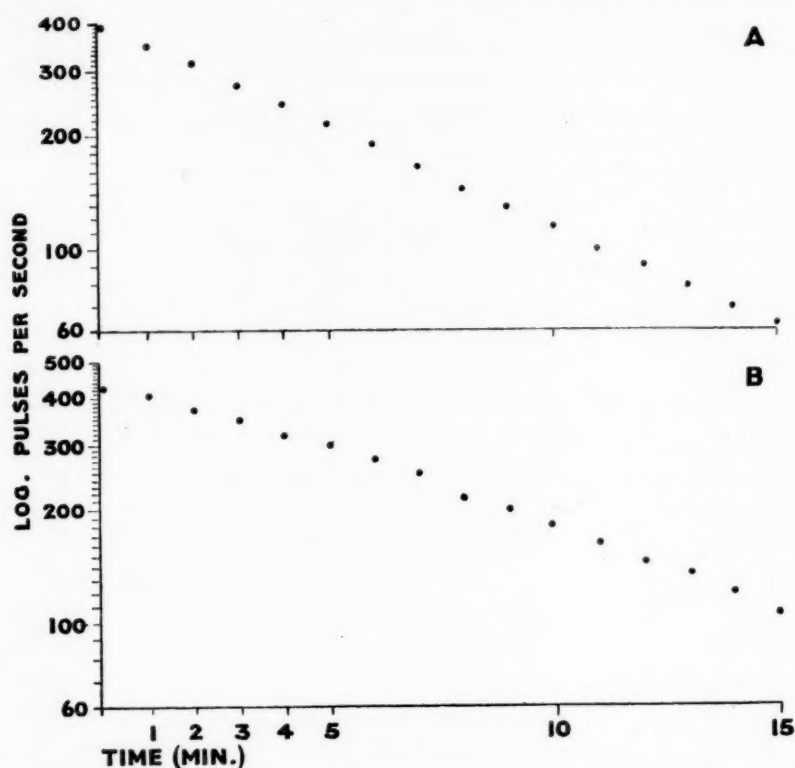


Fig. 2.—Clearance of radioactive sodium from blebs and immediately surrounding area (A) with and (B) without hyaluronidase in a normal subject.

#### Discussion

On raising an intradermal bleb by injection of an isotonic solution, the tensile elements in the skin are stretched and the elastic recoil of these structures is presumably the force responsible for flattening out the bleb. The rate at which this occurs will depend on the balance between this force and the forces resisting the restoration of the normal skin contour, namely the frictional resistance to flow of the injected solution provided by the macro molecules of the ground substance and the fibrous elements of the dermal connective tissue (Fessler, 1957), and the viscosity of the ground substance preventing flattening and "sinking in" of the bleb which might occur with relatively little flow of the solution from the injection site.

The force required to make an intradermal injection and the amount of injected fluid extruded along the path of the needle are usually greater in sclerodermatous than in normal skin. This suggests that the more rapid disappearance of the saline blebs observed in the patients with systemic sclerosis may in part be due to an increased elastic resistance to deformation of sclerodermatous skin.

Acceleration of the rate of disappearance of the blebs by hyaluronidase might be anticipated from the observations of Day (1952) and from the known *in vitro* effect of the enzyme in decreasing the viscosity of solutions of mucopolysaccharides of the connective tissue ground substance. Day showed that the rate of flow of saline through a membrane of mouse connective tissue was increased ten to twenty times by hyaluronidase. He suggested that the ground substance of connective tissue consists of a network of protein fibrils "waterproofed" by impregnation with molecules or molecular aggregates of hyaluronic acid, and that the effect of hyaluronidase in increasing permeability of the tissue was due to removal of these molecules and the opening up of spaces through which the saline could flow. The results of the experiments in which radioactive sodium was employed suggest, how-

ever, that the main effect of hyaluronidase may be to decrease the viscosity of the ground substance and thus allow the bleb to flatten out with relatively little flow of the injected solution away from the site of injection. It was found that arrest of the blood flow through the skin resulted in cessation of sodium clearance, but, in other experiments, arrest of the blood flow was found to have no effect on the rates of disappearance of the blebs. Moreover, the rates of disappearance of sodium from the injection sites bore no direct relationship to the rates of disappearance of the palpable blebs either with or without hyaluronidase, so that the more rapid restitution of the normal skin contour with hyaluronidase must have occurred with relatively little transport of sodium from the vicinity of the injection site, and it is unlikely that any substantial transport of water of the injected saline could occur without movement of the sodium. A decrease in the viscous resistance of the tissue might be expected to allow the volume of fluid contained in the palpable part of the bleb to be accommodated by a relatively slight lateral spread and possibly some "sinking in" of the bleb.

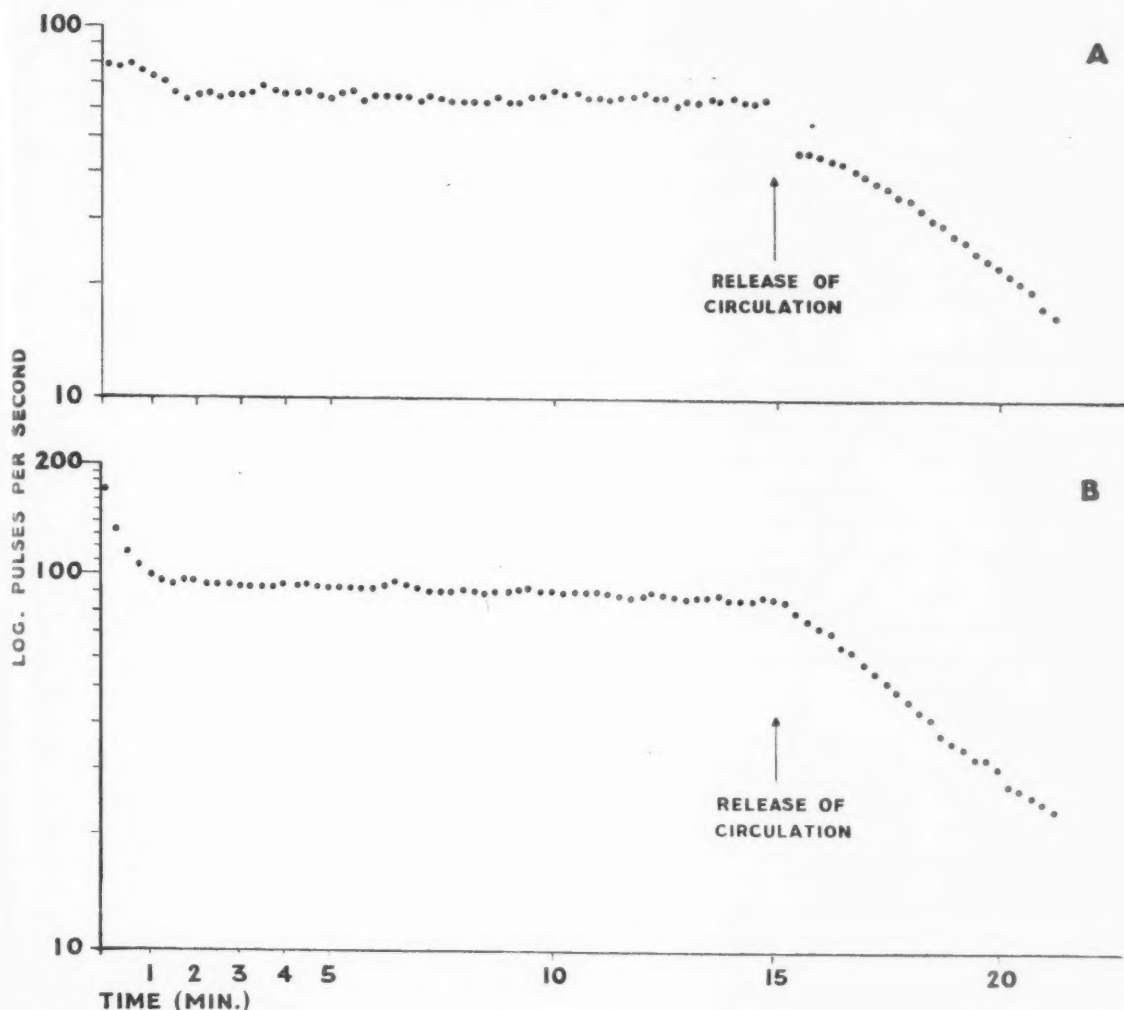


Fig. 3.—Effect of occlusion of arterial circulation on clearance of radioactive sodium from centre of blebs (A) with and (B) without hyaluronidase in a normal subject.

The most probable explanation of the delay in disappearance of the blebs containing hyaluronidase in sclerodermatous skin would appear to be that there is in this condition either a quantitative reduction of the mucopolysaccharides of the ground substance or a qualitative change rendering them insusceptible or inaccessible to the enzyme. Preliminary results of electron-microscopic studies (Chapman and Peach, unpublished data) suggest that the amorphous material surrounding the collagenous fibres in the deeper layers of the dermis is reduced in quantity. The hyaluronic acid of normal synovial fluid is thought to function as a

lubricant of the joint surfaces (Gardner, 1950), and it is possible that the mucopolysaccharides of connective tissue may play a similar role in facilitating movements between its constituent fibres. Loss of mobility in the skin and gastro-intestinal tract is a striking clinical feature of systemic sclerosis, and a characteristic silky "squeaking" crepitus can frequently be felt on movement of joints, tendons, and bursae at many sites; in one case observed *post mortem* there was increased frictional resistance when the finger was passed over the surfaces of these structures. The abnormality of the ground substance in systemic sclerosis may not therefore be

confined to affected skin, but may be a feature of the connective tissue disorder in other affected structures.

### Summary

The duration of the palpable blebs produced by the intradermal injection of physiological saline with and without added testicular hyaluronidase was observed in normal subjects and in patients with systemic sclerosis, dermatomyositis, rheumatoid arthritis, ankylosing spondylitis, or other connective tissue diseases.

In normal subjects the rate of disappearance of the blebs was greatly accelerated by the addition of hyaluronidase. The rate of disappearance was accelerated by raising the skin temperature and retarded by lowering it, but was little affected by variations in the volume of injection (between 0.03 and 0.1 ml.) or by cutting off the skin circulation. The clearance of radioactive sodium from the injection sites was only slightly accelerated by hyaluronidase. When the skin circulation was occluded, the clearance of sodium from the centre of a saline bleb ceased and there was only a barely detectable clearance when the bleb contained hyaluronidase.

In patients with systemic sclerosis, the blebs containing hyaluronidase usually persisted longer and the saline blebs disappeared more rapidly than in normal subjects; the hyaluronidase appeared to be less effective in those with less advanced skin changes. In almost all patients with diseases other than systemic sclerosis, the addition of hyaluronidase resulted in a normal or increased acceleration of the rate of disappearance of the blebs.

The findings suggest that, in systemic sclerosis, there is either a reduction in the amount or a qualitative abnormality of the ground substance of the dermal connective tissue.

We are greatly indebted to Prof. J. H. Kellgren for useful advice and discussion, to Dr. J. Ball, who carried out the sheep cell agglutination tests, and to Miss Freda Bier for assistance with the statistical tests. Drs. S. K. Bannerjee, E. W. Emery, and R. Harris gave much advice and assistance in the radioactive sodium studies.

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### Barrière cutanée dans la sclérose généralisée et dans d'autres maladies rhumatismales

#### RÉSUMÉ

On étudia la durée des bulles palpables provoquées par l'injection intradermique d'eau physiologique, avec ou sans hyaluronidase testiculaire, chez des sujets normaux et chez des malades atteints de sclérose généralisée, dermatomyosite, arthrite rhumatismale, spondylarthrite ankylosante et autres maladies du tissu conjonctif.

Chez des sujets normaux, l'adjonction d'hyaluronidase faisait disparaître les bulles plus rapidement. Cette disparition était accélérée par l'augmentation de la température cutanée et ralentie pas sa diminution, mais était peu influencée par le volume injecté (entre 0,03 et 0,1 c.c.) ou par l'interruption de la circulation cutanée. L'élimination du sodium radioactif de l'endroit de l'injection était à peine accélérée par l'hyaluronidase. L'occlusion de la circulation cutanée arrêtait l'élimination du sodium du centre de la bulle d'eau physiologique; avec l'hyaluronidase il n'y avait qu'une ébauche d'élimination.

Chez des malades atteints de sclérose généralisée, les bulles à l'hyaluronidase persistaient généralement plus longtemps et les bulles à l'eau physiologique disparaissaient plus rapidement que chez des sujets normaux; l'hyaluronidase paraissait moins efficace quand la maladie de la peau était peu avancée. Chez presque tous les malades souffrant de maladies autres que la sclérose généralisée, l'adjonction d'hyaluronidase faisait disparaître les bulles à une vitesse normale ou accélérée.

Ces résultats suggèrent que, dans la sclérose généralisée, la substance de fond de tissu conjonctif de la peau est soit réduite quantitativement soit altérée qualitativement.

### Barrera cutánea en la esclerosis generalizada y en otras enfermedades reumáticas

#### SUMARIO

Se estudió la duración de las ampollas palpables provocadas por inyecciones de suero artificial, con o sin añadidura de hialuronidasa testicular, en sujetos normales y en enfermos con esclerosis generalizada, dermatomiositis, artritis reumatoide, espondilartrosis anquilosante y otras enfermedades del tejido conjuntivo.

En los sujetos normales, las ampollas desaparecían rápidamente en presencia de hialuronidasa. Esta desaparición era acelerada por una aumentación de la temperatura de la piel y retrasada por su disminución, pero el volumen inyectado (entre 0,03 y 0,1 c.c.) o la interrupción de la circulación cutánea no tuvieron efecto alguno sobre la duración de las ampollas. La eliminación del sodio radioactivo del sitio de inyección fué poco acelerada por la hialuronidasa. La oclusión de la

circulación cutánea paró la eliminación de sodio del centro de la ampolla con el suero artificial; con hialuronidasa la eliminación fué poquísima.

En los enfermos con esclerosis generalizada, las ampollas con hialuronidasa persistían generalmente más tiempo y las ampollas con suero artificial desaparecían más rápidamente que en los sujetos normales; la hialuronidasa parecía ser menos eficaz en pieles con enfer-

medad poco adelantada. En casi todos los sujetos con enfermedades otras que la esclerosis generalizada, la hialuronidasa hacía desaparecer las ampollas con una velocidad normal o mayor.

Estos resultados sugieren que, en la esclerosis generalizada, la substancia de fondo del tejido conjuntivo de la piel está reducida cuantitativa o alterada cualitativamente.



## PRODUCTION OF L.E. CELLS *IN VIVO* BY TRANSFUSION OF SYSTEMIC LUPUS ERYTHEMATOSUS PLASMA

BY

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The plasma of patients suffering from systemic lupus erythematosus (S.L.E.) contains a factor which leads to L.E.-cell formation if normal bone-marrow or white blood cells are tested with this plasma *in vitro* (Haserick, Lewis, and Bortz, 1950).

This L.E. factor can be found not only in plasma, but in various other body fluids, such as the cerebrospinal, pleural, and pericardial fluid (Bencze, 1956), in urine, and in cantharides pustules. This L.E. factor passes the placenta barrier, and Bridge and Foley (1954) have observed L.E. cells in the peripheral blood of a baby whose mother suffered from S.L.E.

Hitherto, the successful transmission of the plasma factor and the production of L.E. cells in normal persons *in vivo* has not been reported, nor have any such experiments been successful in animals. The present paper reports the production of the L.E.-cell phenomenon in patients without collagen disease after the transfusion of S.L.E. plasma.

### Method

Plasma was obtained from a patient suffering from S.L.E. (of blood group AB), in whose peripheral blood L.E. cells had repeatedly been observed (Fig. 1). The blood was taken under sterile conditions, using 16 ml. citrate to 100 ml. blood, kept for 24 hrs at  $-4^{\circ}\text{C}$ ., and centrifuged. The blood thus obtained was always L.E.-cell positive, as demonstrated by the rotatory method of Zinkham and Conley (1956) and the ring method of Snapper and Nathan (1955).

### Experiments

(1) A man aged 24 (blood group B), in whom the diagnosis of Hodgkin's disease had been verified histologically, received 200 ml. of this S.L.E. plasma. The transfusion was uneventful. L.E. cells had never previously been found in his blood,

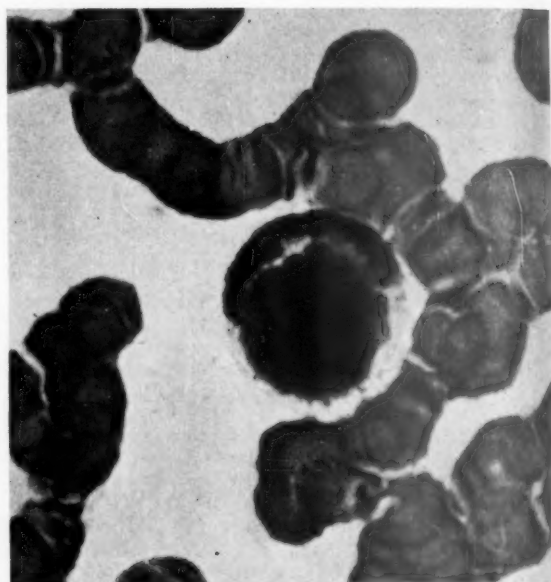


Fig. 1.—L.E. cell of a patient with systemic lupus erythematosus.

but 2 hours after the transfusion the peripheral blood contained many L.E. cells, which reached their maximum 6 to 24 hours later. 11 days after the transfusion, L.E. cells could only be observed occasionally, but they could still be recognized even 27 days later (Figs 2 and 3, opposite). As a control, 35 days later, the same patient was given 400 ml. normal plasma (blood group AB), obtained in exactly the same way as the S.L.E. plasma. The transfusion was uneventful. L.E. cells were searched for 30 minutes, 2, 4, 6, 24, and 48 hours after the transfusion, but without success.

(2) A man aged 72 (blood group O), with a diagnosis of carcinoma of the prostate with metastases, received 200 ml. S.L.E. plasma. L.E. cells had not previously been found in this patient's blood,

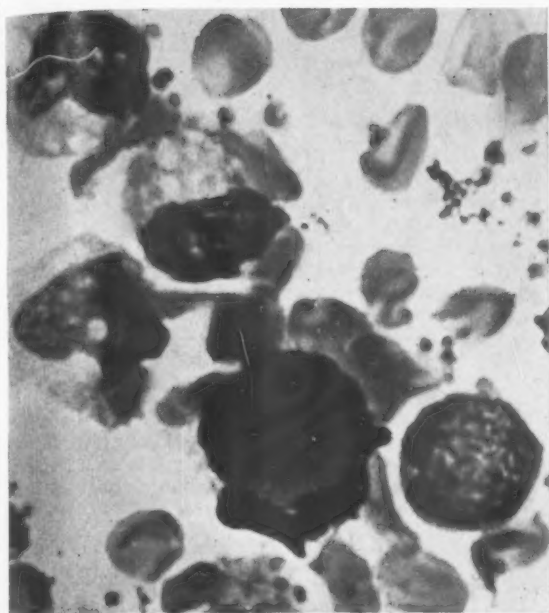


Fig. 2.—L.E. cells in peripheral blood of receptor 24 hours after transfusion.

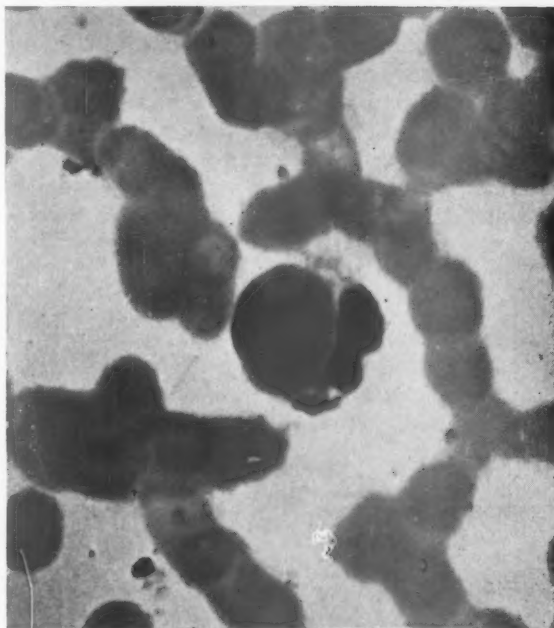


Fig. 4.—L.E. cells in peripheral blood of receptor 24 hours after transfusion.

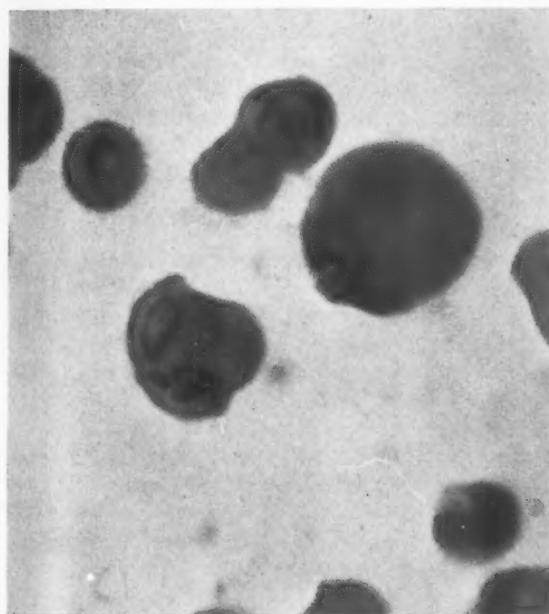


Fig. 3.—L.E. cells in peripheral blood of receptor 27 days after transfusion.

(3) A woman aged 52 (blood group A), with a diagnosis of carcinoma of the ovary with metastases, received 140 ml. S.L.E. plasma. No L.E. cells had previously been observed in her blood. After the transfusion she developed a chill and her temperature rose to  $39^{\circ}\text{C}$ ., but she soon recovered without other complications. Her peripheral blood contained a striking number of L.E. cells and 10 days later they were still numerous.

#### Discussion

The L.E.-cell phenomenon has been produced in the blood of three patients suffering from conditions other than collagen disease by transfusing plasma from a patient with S.L.E. In all three, many typical L.E. cells could be observed as early as 2 hours after the transfusion, and for 10 days afterwards, the maximum being seen from 6 to 24 hours after the transfusion. The number of induced L.E. cells surpassed that in the blood of the donor patient. In one case, 60 to 80 L.E. cells per 1,000 leucocytes were present as compared with 30 to 40 per 1,000 granulocytes in a smear from the donor. From the eleventh day L.E. cells were found only occasionally, but in the first case a few could still be observed after 27 days.

These experiments prove that plasma from S.L.E. patients contains a factor which is responsible for the formation of L.E. cells, and which enables the L.E.-cell phenomenon to be reproduced in other

but 2 hours after the transfusion the peripheral blood contained a large number of L.E. cells, which reached their maximum 6 to 24 hours later (Fig. 4). After 24 hours their number slowly decreased; some could still be found on the tenth day, but from the eleventh day only occasional L.E. cells were observed.

subjects. Up to now the existence of the L.E. factor in plasma has been demonstrated only *in vitro* by treating normal bone marrow or white blood cells with S.L.E. plasma. The present experiments have proved the transmission of L.E. factor by producing L.E. cells in persons without S.L.E.

Future experiments will aim at discovering whether the plasma factor can be held responsible for any changes occurring in S.L.E.

#### Summary

200 ml. plasma from an L.E.-cell positive woman was administered to three patients with malignant disease, in whom L.E. cells formed almost at once, with a maximum between the 6th and 24th hours.

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#### Production des cellules L.E. *in vivo* par transfusion du plasma affecté par lupus érythémateux généralisé

##### RÉSUMÉ

On administra à trois femmes atteintes d'une maladie maligne 266 c.c. de plasma provenant d'une femme chez qui on avait démontré la présence de cellules L.E. Les transfusés formèrent des cellules L.E. presque immédiatement, avec un maximum entre la 6ème et la 24ème heure.

#### Producción de células L.E. *in vivo* por transfusión de un plasma con lupus eritematoso generalizado

##### SUMARIO

Se administraron a tres mujeres afectas de una enfermedad maligna 266 c.c. de plasma procediendo de una mujer con células L.E. comprobadas. Las receptoras formaron células L.E. casi inmediatamente, con un máximo entre las 6 y las 24 horas.

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## ELECTROPHORETIC ANALYSIS OF SERUM PROTEIN IN REITER'S SYNDROME

BY

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Reiter's syndrome is a condition of unknown aetiology, but is probably of infective origin, with the primary focus in the genital tract. It occurs characteristically in young men in association with non-specific urethritis, arthritis, and conjunctivitis. In the course of time other features were noted to be sometimes associated, including haemorrhagic cystitis, iritis, sacro-iliitis, ankylosing spondylitis, balanitis, stomatitis, keratoderma blenorrhagica, and other skin lesions. *Formes frustes* are also recognized, of which the combination of non-specific urethritis and arthritis alone is the commonest. The natural history of these clinical types of the syndrome appears to be essentially the same (Csonka, 1958).

The attacks are usually of acute onset and of a few months duration, but recurrences or relapses are common and in some cases the condition becomes sufficiently severe and chronic to be mistaken for rheumatoid arthritis.

This paper is concerned with the electrophoretic pattern of serum proteins obtained in thirty consecutive male patients with Reiter's syndrome. As a control, the sera of 27 healthy medical students and ten cases of rheumatoid arthritis were examined by the same method.

In the patients with Reiter's syndrome, the protein estimations were repeated at different stages of the disease; the remainder had single tests. None of the patients with Reiter's syndrome had albuminuria and there was no evidence of liver disease. Although there is, as yet, no specific treatment for this condition, all the patients were having treatment with one of the broadspectrum antibiotics and analgesics, four were having phenylbutazone. Fever

therapy or steroids were only given after the specimens had been obtained for electrophoresis. None of the patients with rheumatoid arthritis were on cortisone treatment when the electrophoresis of the serum proteins was undertaken.

### Method

The total protein was determined by the biuret method, results being read from a standard graph on which the biuret values for total protein had been checked by Kjeldahl N determinations. Electrophoresis was carried out in the Bridge Unit described by Kawerau (1954). Satisfactory resolution of alpha-one globulin from albumin was obtained in every case. It has been our experience that apparatus of different design, *e.g.* vertical tanks, does not give such a satisfactory separation in this region. A rigid technique giving an overall separation of 13-14 cm. was adhered to in the course of this investigation. It has been shown by Kohn (1957) that separation of alpha-one globulin from albumin is much improved on cellulose acetate strips, but unfortunately this material was not available when this work was begun. Quantitative evaluation of the electropherograms was undertaken after the strips had been rendered translucent by impregnation with benzyl alcohol and by photo-electric scanning of 1-mm. cross-sections of the strips with the apparatus described by Grassman, Hannig, and Knedel (1951). The protein areas of the graphs so obtained were measured with the planimeter, and each one was expressed as a percentage of the total area. Absolute values for the globulin fractions were not calculated from the relative percentage figures, as there is some objection to this procedure (Durrum, 1956), and in this particular investigation it would not have increased the accuracy of the calculations significantly, for the total protein values in the groups that were compared varied only over a narrow range.



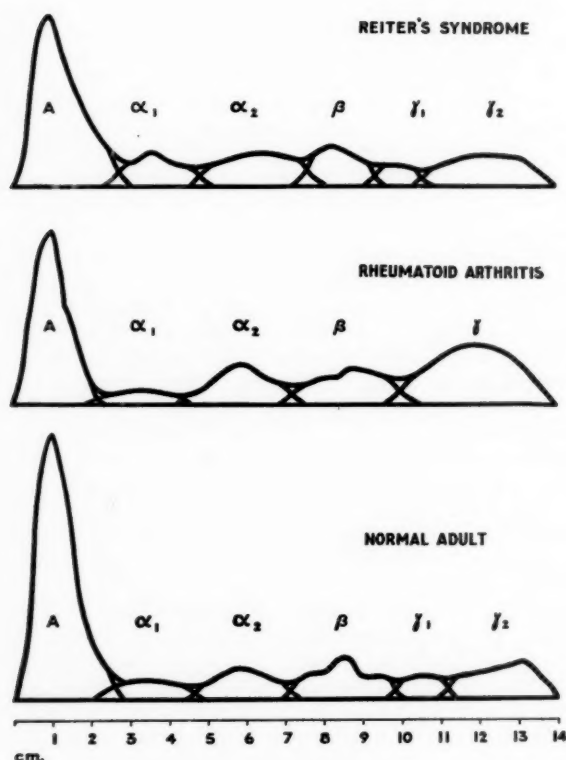
## Results

Characteristic electropherograms are shown in Fig. 1. The sera belong to patients who suffered an exacerbation of the chronic form of the respective illnesses. The high alpha globulins in Reiter's syndrome and the high gamma globulin in rheumatoid arthritis are the most distinguishing features. The pattern for Reiter's syndrome often looks more dramatically abnormal than it appears here, but this choice has been deliberate in order to emphasize the difficulty inherent in the technique. Casual inspection may not reveal the abnormality. A protein spread of over 13-14 cm. is required and careful planimetric evaluation is needed before significant alterations in the alpha-one proteins can be detected. It must be emphasized here that investigators employing different apparatus and technique may not obtain comparable results. When results by different techniques are compared, the determining factor is the total distance that the albumin travelled (on account of albumin training), the sharpness of resolution, and the type of dye used for the staining. As this communication is not primarily intended for a discussion of the technique

of paper electrophoresis, the reader is referred to the bibliography for further information.

Table I and Fig. 2 (opposite) summarize the statistical analysis of the results, assuming that the distribution of the normal concentration of the protein fractions follows a normal distribution curve, and that therefore 95 per cent. of all normal values will lie within a range of two standard deviations (S.D.) above and below the mean volume for each fraction. To estimate whether the mean of the protein fractions from Reiter's patients differs significantly from the mean of the control group, the "t" test is used. A value of 5 per cent. has been selected as level of significance, *i.e.* values of greater magnitude would occur by chance only once in twenty times.

As the results are expressed as percentage of total protein, a change in one fraction will lead to complementary changes in the percentage distribution of all other fractions; thus a decreased concentration of albumin results in an increased percentage of *all* globulin fractions, and an abnormal increase in a particular globulin fraction can only be considered under these circumstances, if it exceeds the expected rise, or total protein is increased.



Protein Percentage

A	50.6
$\alpha_1$	9.4
$\alpha_2$	16.4
$\beta$	6.9
$\gamma_1$	5.4
$\gamma_2$	11.3

A	40.4
$\alpha_1$	3.4
$\alpha_2$	11.8
$\beta$	13.2
$\gamma$	31.2

A	64.0
$\alpha_1$	4.9
$\alpha_2$	10.3
$\beta$	9.1
$\gamma_1$	3.3
$\gamma_2$	8.4

Fig. 1

ELECTROPHORETIC ANALYSIS OF SERUM PROTEIN IN REITER'S SYNDROME 431

TABLE I  
ELECTROPHORETIC SERUM PROTEIN FRACTIONS IN REITER'S SYNDROME AND HEALTHY CONTROLS<sup>i</sup>

Series	No. of Patients	Total Protein (g./100 ml.)	Albumin (% Total Protein)	Globulin (% Total Protein)				
				$\alpha_1$	$\alpha_2$	$\beta$	$\gamma_1$	$\gamma_2$
Controls .. ..	27	Mean $\pm$ 2 S.D. 8.0 6.6-9.4	63.8 52.8-74.8	3.8 1.2-6.4	7.0 2.6-11.4	10.6 6.0-15.2	5.4 1.3-9.3	9.4 4.9-14.3
Reiter's Syndrome .. ..	30	Mean 7.4 Signif. (p)	48.3 0.001	7.3 0.001	12.1 0.001	13.5 0.01	6.9 0.05	12.3 0.01

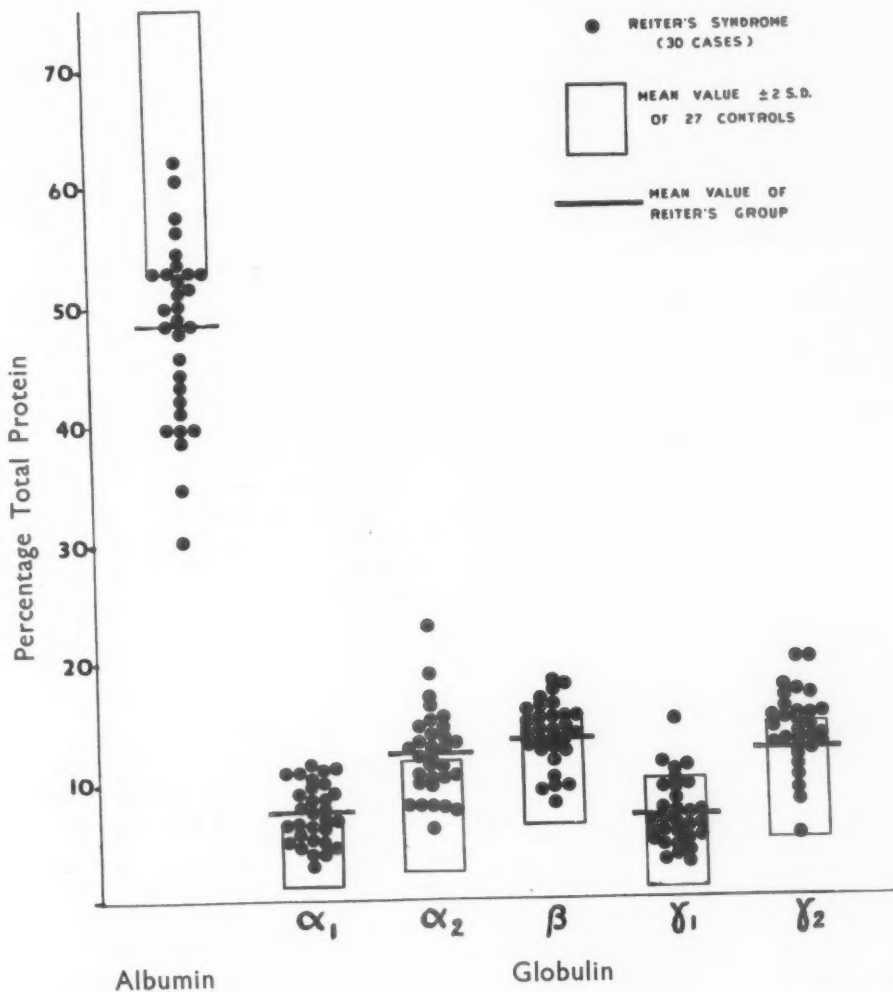


Fig. 2.

The total protein of the Reiter's patients did not significantly differ from the control group. A significant degree of hypo-albuminaemia was found in 24 of the thirty patients and was at the lower level of the normal range in the remaining six. Of the

globulin fractions,  $\alpha_1$  was significantly raised in nineteen cases and was at the upper limit of the normal range in three;  $\alpha_2$  was significantly raised in eighteen cases with five more at the upper limit of normal. The  $\beta$  globulin showed a less marked

rise, which affected ten sera. The  $\gamma_1$  and  $\gamma_2$  globulins were significantly raised in five and twelve sera respectively.

In Table II the cases are separated according to the clinical severity and activity of the illness. The changes in the protein fractions in the severe cases are more marked than in the less severe ones, but in both groups the direction of these changes from the normal is the same, *i.e.* towards hypo-albuminaemia, raised  $\alpha$  and  $\gamma$  globulins, and a less constant increase in the other globulins. The third group consisted of patients judged to be convalescent when the protein fractions were estimated; the main abnormalities were a decrease in albumin and an increase in the globulin concentration, but these changes were smaller than in the other groups which contained the active cases.

An analysis of the protein pattern according to the duration of the syndrome, which ranged from one week to several years, showed no significant changes related to duration, provided due regard to clinical severity was made; thus a long but mild attack produced protein changes similar to those seen in a short but mild attack, and a severe attack was commonly associated with the more marked changes in the albumin and  $\alpha$  globulin fractions, irrespective of its duration.

Serial Electrophoretic Serum Protein Estimations

In fourteen cases of Reiter's syndrome the tests were repeated at different times during the illness. 36 sera were examined and significant hypo-albuminaemia and raised globulin concentration were seen to be present as early as the seventh day after the onset of arthritis (or the sixteenth day of urethritis). These changes were slow to return towards normal after the attack was over, and in one case the abnormalities were still present one year after the acute attack had subsided. Of particular interest were four chronic cases, which were, at one time, thought to suffer from rheumatoid arthritis.

Serial tests were performed over a period of 8 to 23 months; the results are shown with representative examples of other patients in Table III (opposite). This corroborates the impression formed from single estimations in patients taken at different phases of the illness, and shows that the changes in the protein fractions are correlated with the severity rather than with the duration of the disease, and that these abnormalities are reasonably constant over a period of time and distinct from those generally accepted as characteristic for rheumatoid arthritis (see Discussion).

Correlation with the Erythrocyte Sedimentation Rate

The erythrocyte sedimentation rate (Westergren) was estimated simultaneously with the serum electrophoresis (Table IV, opposite). Correlation between the E.S.R. and electrophoretic protein changes was good, but a few discrepancies occurred. Correlation between these tests and the clinical status was best in the group of cases judged to be severely affected. Both the raised E.S.R. and the abnormal protein pattern were independent of body temperature.

The group of patients with rheumatoid arthritis was not analysed in great detail, on account of their small number. The clinical history of these patients showed, however, that one was dealing with all stages of the disease, with respect both to the duration and to the severity of the illness. The significant rise in gamma globulins in this group of patients, as compared with that in the Reiter's syndrome group, is not a chance finding, as the statistical analysis shows (Table V, opposite).

Discussion

There is scanty information in the medical literature on the electrophoretic serum protein fractions in Reiter's syndrome. Svartz and Olhagen (1948) found an increase in alpha globulin and a

TABLE II  
MEAN ELECTROPHORETIC VALUES IN THIRTY CASES OF REITER'S SYNDROME,  
BY CLINICAL SEVERITY AND ACTIVITY OF DISEASE

Clinical Group	No. of Patients		Albumin (per cent.)	Globulin (per cent.)				
				$\alpha_1$	$\alpha_2$	$\beta$	$\gamma_1$	$\gamma_2$
Severe .. .. .	14	Mean ± 2 S.D.	42.7 31.3-54.1	8.6 4.0-13.2	14.3 7.6-21.0	14.1 9.9-18.3	7.8 1.6-14.0	12.6 6.9-18.3
Mild .. .. .	9	Mean ± 2 S.D.	52.4 43.5-61.3	6.9 3.7-10.1	11.2 5.4-17.0	11.7 5.6-17.8	6.1 4.8-7.4	11.9 3.1-20.7
Convalescent .. .. .	7	Mean ± 2 S.D.	54.4 47.9-60.9	5.2 1.8-8.6	8.9 5.6-12.2	13.8 9.2-18.4	5.8 1.3-14.3	12.0 8.0-16.0

## ELECTROPHORETIC ANALYSIS OF SERUM PROTEIN IN REITER'S SYNDROME 433

TABLE III  
SERIAL ELECTROPHORETIC PROTEIN TESTS IN SEVEN CASES OF REITER'S SYNDROME

Case No.	Date of Test	Clinical Status	Erythrocyte Sedimentation Rate (mm./hr Westergren)	Serum Protein Fractions (per cent.)					
				Albumin	Globulin				
					$\alpha_1$	$\alpha_2$	$\beta$	$\gamma_1$	$\gamma_2$
1	10.4.56	Acute severe attack of 2 weeks' duration End of convalescence; fit to work	30	47.7	10.1	12.7	15.2	3.6	10.7
	8.10.56		5	54.5	4.5	10.0	15.2	4.8	11.0
2	23.3.56	Acute severe attack of one week's duration Symptom-free one year after end of attack	108	49.6	4.9	18.9	13.2	4.9	8.5
	19.6.57		5	50.6	9.4	16.4	6.9	5.4	11.3
3	12.10.56	Acute mild attack of 10 days' duration Improving Symptom-free for 8 months Recurrence of arthritis lasting one week	32	46.0	9.7	14.7	12.8	4.4	12.4
	29.10.56		14	46.3	5.0	15.2	13.5	7.6	12.4
	17.7.57		5	51.8	7.0	9.6	11.9	4.1	15.6
	23.8.57		30	44.2	8.1	13.8	17.0	6.0	10.9
4	16.3.56	Chronic severe illness; duration 15 years; at present quiescent Greatly increased activity Improving; slight activity in joints	4	57.6	4.4	11.1	12.9	4.2	9.9
	14.6.57		15	42.0	8.5	13.9	14.0	9.1	12.5
	21.3.58		12	56.5	5.8	11.8	10.2	4.7	11.0
5	3.3.56	Chronic mild illness; duration 12 years Improving; slight activity in joints	20	54.5	4.0	9.1	13.3	7.1	12.0
	10.4.57		6	51.1	5.5	8.8	16.8	6.9	11.0
6	28.12.55	Acute severe attack of 2 months' duration Slight improvement Joints still active No change Joints better; iritis troublesome Sacro-iliitis radiologically confirmed; joints active	135	39.8	4.1	12.7	13.2	10.1	20.1
	1.2.56		103	36.9	6.2	13.4	12.4	7.0	24.0
	16.11.56		52	38.5	6.2	14.5	16.2	9.2	15.4
	25.1.57		50	35.3	7.6	14.6	19.5	7.9	15.1
	8.7.57		60	51.0	6.8	10.9	12.9	5.1	13.3
	6.1.58		15	54.3	7.5	13.4	10.0	13.8	
7	19.10.56	Chronic severe illness; duration 13 years No change Activity increasing; new joints involved	50	47.0	5.3	8.2	14.6	6.1	18.4
	1.11.56		19	43.0	6.5	13.5	14.4	5.5	17.1
	29.5.57		20	34.5	11.2	13.6	9.5	14.8	16.4

TABLE IV  
ERYTHROCYTE SEDIMENTATION RATE AND SERUM PROTEIN CHANGES

Clinical Status of Reiter's Syndrome	No. of Patients	Erythrocyte Sedimentation Rate (mm./hr Westergren)		Electrophoretic Serum Protein Pattern	
		0-15	>15	Normal	Albumin Significantly Reduced $\alpha$ -Globulin Significantly Raised
Severe .. .. .	14	2	12	1	13
Mild .. .. .	9	4	5	4	5
Convalescent .. .. .	7	4	3	6	1

TABLE V  
ELECTROPHORETIC SERUM PROTEIN FRACTIONS IN REITER'S SYNDROME AND RHEUMATOID ARTHRITIS

Series	No. of Patients	Total Protein (g./100 ml.)	Albumin (per cent.)	Globulin (per cent.)			
				$\alpha_1$	$\alpha_2$	$\beta$	$\gamma^*$
Reiter's Syndrome .. .. .	30	Mean	48.3	7.3	12.1	13.5	19.0
		$\pm$ 2 S.D.	33.9-62.7	2.6-12.0	5.0-19.2	7.9-19.1	8.4-29.6
Rheumatoid Arthritis .. .. .	10	Mean	41.1	6.4	12.4	12.5	28.0
		Signif. (p)	Nil				

\* Expressed as  $\gamma$ -globulin, as not every serum in rheumatoid arthritis could be separated into  $\gamma_1$  and  $\gamma_2$  globulin.

decrease in albumin concentration in three such patients. Ropes, Perlmann, Kaufman, and Bauer (1954) found similar changes in two cases, and Laurell (1956) reported a significant increase in the alpha-two globulin in the presence of low albumin concentration in three cases. Our observations are in agreement with those of these authors.

Of the 23 patients with active disease, nineteen showed a significant rise in the alpha globulins, which was slightly more marked in the alpha-one fractions. That this increase in the alpha proteins is due to an increase of glycoproteins was shown by Laurell (1956), who determined the hexose content of the alpha proteins in his cases of Reiter's syn-



drome. Serum alpha-two glycoprotein increases have been shown by Sary, Bodur, and Batiyok (1951) and by Jayle (1946) to move parallel with the E.S.R. A similar parallelism has been observed in our cases. Jayle has gone further and linked E.S.R. increases with rises in the alpha-two haptoglobulin glycoprotein of serum in various forms of disease. Whether or not the alpha-two globulin increases in Reiter's syndrome are synonymous with raised haptoglobulin levels remains, at present, uncertain, and may be a problem worthy of further investigation.

Recent studies in the clinical interpretation of quantitative paper electrophoresis (Antweiler, 1957; Jencks, Smith, and Durrum, 1956) show that the combination of low albumin and high alpha globulins, with little change in the other globulin fractions, is not a specific pattern for Reiter's syndrome, as similar changes have been noted in many other conditions, mainly infectious. It is evident from this study, however, that, though the pattern may not be specific, it is characteristic for Reiter's syndrome and persists at least as long as the disease can be judged on clinical grounds to be active. Sera obtained months or even years after urethral and eye symptoms have subsided show the characteristic electrophoretic protein changes, and there is, therefore, no evidence that the protein changes depend on the persistence of the genital infection.

In the diagnosis of Reiter's syndrome, rheumatoid arthritis has sometimes to be considered. Some authorities, in fact, have suggested that one may be dealing with rheumatoid arthritis which has been precipitated by the genital infection (Hench and Boland, 1946; Hench and others, 1948; Balboni and Kydd, 1952). It is therefore of interest to compare our findings in Reiter's syndrome with the recent literature on the serum proteins in rheumatoid arthritis.

Two main patterns have been described:

(1) Raised alpha and gamma globulin (Svartz and Olhagen, 1948; Wallis, 1950; Ropes and others, 1954; Hunt and Trew, 1954; Laurell, 1956; Bonomo, 1957).

(2) Raised gamma globulin as the outstanding or sole globulin abnormality (Browning, Rice, and Ulrich, 1951; Layani, Bengui, and Mende, 1952; Olhagen, 1952; Jencks and others, 1956; Schlegel, Behrend, and Eggstein, 1956; Laurell, 1956).

It is generally thought that the increase in the alpha globulin is associated with the early inflammatory exudative stage of rheumatoid arthritis, whereas the increase in gamma globulin appears later during the chronic fibrotic stage (Olhagen, 1952; Ropes and others, 1954; Bonomo, 1957).

An analysis of the results in our own cases of rheumatoid arthritis, though not acceptable as a series in themselves, furnishes some support for the published data of other workers. The rise in the alpha globulins was most marked in the acutely-ill patient at the onset of the disease, the gamma globulin rise dominating the field in the chronic and moderately-ill patient. There is some evidence in our data to support the idea that the rise in alpha globulin completely subsides as the condition becomes chronic (fibrotic). Four out of the ten patients with rheumatoid arthritis, in whom a rise of gamma globulins was the sole abnormality of the protein pattern, were only moderately ill and had suffered from the disease for some years.

Our series of patients with Reiter's syndrome covered a wide range in respect of severity and duration, and therefore the rarity of a significantly raised gamma globulin is noteworthy. In the individual case, electrophoretic analysis may not be of great value in differentiating rheumatoid arthritis from Reiter's syndrome, but the results of larger series give sufficiently distinct patterns to support those who wish to regard the two conditions as separate entities.

### Summary

Electrophoretic serum protein estimations in thirty patients with Reiter's syndrome, ten patients with rheumatoid arthritis, and 27 healthy controls are presented.

The most consistent protein pattern in Reiter's syndrome showed hypo-albuminaemia and a raised alpha globulin. These findings are thought to be characteristic for the condition, though not specific. Beta and gamma globulins were less markedly or consistently elevated. The pattern was distinct from that found in rheumatoid arthritis in the present investigation.

The degree of albumin and alpha globulin changes showed a positive correlation with the severity rather than the duration of the illness, the abnormal protein values tending to return to normal during convalescence. In one patient, however, the abnormal pattern persisted for a year after the attack had subsided. The changes in the globulin fractions preceded those in the albumin fractions.

Correlation with the erythrocyte sedimentation rate was close in the active stages of the syndrome and less close during convalescence.

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# Analyse électrophorétique des protéines sériques dans le syndrome de Reiter

## RÉSUMÉ

On procéda à l'étude électrophorétique des protéines sériques chez 30 malades atteints de syndrome de Reiter, 10 d'arthrite rhumatoïdale et 27 témoins.

L'hypo-albuminémie et la globuline alpha augmentée constituèrent le trait le plus constant des protéines dans le syndrome de Reiter. On croit que ce trait est caractéristique, mais non pas spécifique, de cette affection.

L'augmentation des globulines beta et gamma fut moins prononcée et moins fréquente. Le tableau fut différent de celui trouvé dans l'arthrite rhumatoïdale dans le travail présent.

L'intensité des altérations des chiffres d'albumine et de globuline alpha revela une corrélation positive avec la sévérité plutôt qu'avec la durée de la maladie, ces chiffres tendant à devenir normaux pendant la convalescence. Chez un malade, cependant, le tableau anormal persista un an après la fin d'une attaque. Les altérations de la globuline précédèrent celles de l'albumine.

Il y eut une corrélation étroite avec la vitesse de sédimentation érythrocytaire à la période active du syndrome et moins étroite pendant la convalescence.

## Análisis electroforético de proteínas séricas en el síndrome de Reiter

## SUMARIO

Se estudiaron los rasgos electroforéticos de las proteínas séricas en 30 enfermos con el síndrome de Reiter, 10 con artritis reumatoide y 27 testigos.

La hipo-albuminemia y la globulina alfa aumentada constituyeron el rasgo más constante de las proteínas en el síndrome de Reiter. Se cree que este rasgo es característico, pero no específico, de este síndrome. La elevación de las globulinas beta y gama fué menos pronunciada y menos frecuente. El cuadro fué diferente del encontrado en la artritis reumatoide en esta investigación.

La intensidad de las alteraciones en las cifras de albumina y de globulina alfa reveló una correlación positiva más bien con la severidad que con la duración de la enfermedad, tendiendo estas cifras hacia la normalidad durante la convalecencia. En un enfermo, sin embargo, el cuadro anormal persistió un año después un ataque. Las alteraciones de la globulina precedieron las de la albumina.

Hubo una correlación estrecha con la velocidad de la sedimentación eritrocitaria durante el período activo del síndrome y menos estrecha durante la convalecencia.

## ACTIVATION OF DENTAL INFECTIONS BY CORTISONE STUDIES IN CHILDREN WITH RHEUMATIC FEVER

BY

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During a study of factors influencing the rebound phenomenon in rheumatic fever, a high incidence of infections, especially the dental abscess, was found in children treated with cortisone or corticotrophin (Holt, 1956). These dental lesions showed several unusual features, and so that more could be learnt about them and their relationship to the rebound phenomenon, 34 children treated for rheumatic fever since January, 1956, were observed carefully. These children were a consecutive unselected series of patients admitted to the Children's Hospital, Sheffield, under the care of Professor R. S. Illingworth. None was specifically referred because of dental trouble as well as rheumatic fever. No child who satisfied the criteria for the diagnosis of rheumatic fever and received treatment was omitted from this study.

There were fifteen boys and nineteen girls, aged from 5 to 14 years. Cortisone was given to all the children in the following dosage:

Day	Amount (mg./day)
1	300
2-4	200
5-21	100
22-55	75
26-90	50

26 of the children also received salicylates. Treatment with cortisone or with cortisone and salicylates was continued until the erythrocyte sedimentation rate (E.S.R.), determined weekly, had been normal for three consecutive readings. The duration of treatment varied between 3 and 7 weeks in 32 cases, but the other two children were treated

for 13 weeks. This form of therapy for rheumatic fever is discussed more fully elsewhere (Illingworth, Lorber, Holt, and Rendle-Short, 1957). The duration of treatment did not appear to influence the lesions described below and is not considered further.

The detailed observations that have now been completed on these 34 children form the basis of the present report.

### The Dental Lesion

Either during or within a few days of the end of cortisone treatment activation of an already existing periodontal lesion was frequently observed. This occurred particularly where there was advanced caries with the loss of vitality of the tooth, or where there was a loose deciduous tooth with deep periodontal pockets. These activated lesions differed from the usual periapical or periodontal abscess in that pain was slight or absent and swelling was less marked than expected. If swelling was present it was confined to the immediate area of the alveolus and buccal sulcus. In no case was a spread beyond the area with an associated cellulitis observed. Local lymph-node enlargement was detected in only two of the six children developing abscesses. In some of the children the only clinical sign was a flood of pus from the neck of a loose deciduous tooth on pressure—a sign easily missed in a casual examination of the mouth. The condition which we observed is well illustrated by the following case.

### Case Report

A girl aged 12 years was admitted to hospital with fever, malaise, and pain in the right knee of one week's duration. She had had tonsillitis a week earlier.

She looked an ill child. Her temperature on admission

was 100° F. The right knee was swollen and painful to move and to touch. There was a coarse Grade III systolic murmur and a diastolic murmur at the apex of the heart. The electrocardiogram was normal. The throat swab did not show haemolytic streptococci, but the antistreptolysin-O titre was 450 units/ml. The E.S.R. was 65 mm. in the first hour (microWestergren), the C-reactive protein 5+, the mucoprotein tyrosine 13.6 mg./100 ml., and the haemoglobin 9.9 g./100 ml.

She was treated with cortisone and salicylates in high doses. Penicillin was given intramuscularly to eliminate streptococci and then continued orally as a prophylactic. The response was good; after 14 days the E.S.R. was normal (7 mm./hr) and treatment was stopped after 28 days. A week later the E.S.R. rose to 20 mm./1 hr and this coincided with the peak of activation of the dental lesion. Dental extractions were performed and the E.S.R. returned to normal and remained so. The initial dental examination had shown that several deciduous teeth were still present. The radiograph of the lower right first and second deciduous molars is typical of the condition found in these areas (Figure).

One week after admission the alveolus around these teeth became red and oedematous, though the patient complained only once of pain on chewing. These teeth gradually loosened until they could be rocked to and fro, and with each movement a small bead of pus extruded. The organisms isolated from this pus were *Streptococcus viridans* and *Neisseria*.

The 34 children studied were placed into three groups according to their dental condition:

(1) The teeth of eleven children were virtually caries free; there were no deep periodontal pockets and the gingivae were pink, firm, and well attached.



Figure.—Radiograph of lower right first and second deciduous molars.

(2) Four children had deep cavities but their teeth responded to the usual tests for vitality (white and not grey in appearance; sensitive to cold as tested by ethyl chloride and to heat). In doubtful cases a radiograph was taken to assist diagnosis.

(3) There were nineteen children with dead teeth. Four of these had dental extractions early in the course of treatment to prevent dental lesions, and six of the remaining fifteen children (4 girls and 2 boys) developed abscesses either during cortisone treatment or within 2 weeks of stopping it (40 per cent.). These cases are summarized in Table I; in four of them the deciduous teeth had been retained longer than usual and the abscess appeared in the areas of extensive root resorption, and in the other two the lesion was periapical.

TABLE I  
SIX CHILDREN WHO DEVELOPED DENTAL LESIONS

Case Number	Age (yrs)	Sex	Initial Examination	Site of Abscess	Treatment	Comments
1 (described in text)	11	F	ED   Overlong retention of ED   DE deciduous teeth	ED	ED   extracted ED   DE	Pus— <i>Strep. viridans</i> <i>Neisseria</i>
2	7	M	D E   D Carious and non-vital	E	D E   D removed	Pus— <i>Haemophilus</i> <i>Strep. viridans</i> <i>Neisseria</i>
3	9	F	Ten carious teeth E D   non-vital	E D	E D   extracted	
4	8½	F	ED   CDE carious 6ED   DE6	6	6   CDE extracted 6   6 later	
5	9½	M	1 fractured, now dead and with bone loss at apex on radio- graph	1	1 removed	Pus— <i>Strep. viridans</i> <i>Neisseria</i> <i>S. albus</i> (coag. -ve)
6	13½	F	6   6 dead 6   6 No bone change at apex	6   6 	6   6 removed 6   6	Pus from   6 <i>Strep. viridans</i> <i>Neisseria</i> Pus from 6   <i>Diphtheroids.</i> <i>Neisseria</i>



Case 5 is interesting in that the abscess developed in relation to a dead and previously fractured tooth.

The absence of pain with these dental abscesses was very noticeable and was probably due to the facilitation by the cortisone of the diffusion of the infection. Salicylates may also have helped to suppress the symptoms in those children receiving them. The dental lesions were not prevented, however, by the oral penicillin that was given routinely to all the children in treatment of their rheumatic fever.

There is no reason to suppose that this action of cortisone on the dental lesions is limited to children with rheumatic fever. In fact we have seen an identical reaction in a child receiving cortisone for nephrosis.

#### Dental Abscesses and the Erythrocyte Sedimentation Rate

Our attention was originally drawn to the activated dental lesions during a search for causes of the raised sedimentation rate so often observed after the end of cortisone therapy in rheumatic fever. It was then necessary to know whether a relatively small septic lesion could produce this systemic disturbance. The available evidence suggested that it could not do so. Rault (1930) had reported that 85 per cent. of 300 patients with periodontal infections had a raised E.S.R., but this could not be supported by Allard, Ralston, and Ralston (1931) or by Cutler (1932). Lintz (1934) studied the E.S.R.s of 27 patients with periodontal infection, as shown by radiographs or by the presence of an abscess following extraction; 25 of the 27 patients are of particular interest, for their ages ranged from 5 to 15 years. Only one of the 25 had a high E.S.R. (Rourke and Ernstone method).

We were able to confirm by studies on children attending the Charles Clifford Dental Hospital, Sheffield, that periodontal infections in normal children seldom affect the E.S.R. These children were selected at random, and the E.S.R. (micro Westergren) was performed as they were anaesthetized before an extraction. In only ten out of 63 children examined was the E.S.R. raised; it was over 20 mm./hr in eight, and over 30 mm. in two. These ten children had particularly severe lesions, and the E.S.R. was often normal in the presence of acute periodontal infection, and even when raised it did not usually reach the levels often seen in the rebounds of rheumatic fever.

There appeared, however, to be a close association between the elevation of the E.S.R. and the activated dental lesions in the cases under discussion. In all

the 34 children, except two who had dental abscesses, the E.S.R. settled quickly and remained normal throughout cortisone treatment. In Case 5 the E.S.R. became normal within seven days of starting treatment. It became slightly raised on the 24th day and much higher on the 32nd day, but at this time the dental abscess was detected, and after the tooth had been extracted the E.S.R. promptly returned to normal. In Case 6 the E.S.R. did not settle to normal but fluctuated considerably; on the 60th day an acute dental abscess was found and extractions were performed, but the E.S.R. remained raised until the 90th day when a boil in the nose was found and burst. In this case the picture is not as definite, but it is possible that the additional septic focus in the nose helped to keep the E.S.R. high.

In each of the other four children with dental abscesses (Cases 1 to 4), the lesions became active shortly after stopping cortisone therapy and in each case there was a rebound of the E.S.R. Extractions were performed and the E.S.R. settled rapidly in Cases 1 to 3, but in Case 4 the rebound was so severe that it was thought to be advisable to give a second course of treatment.

The response of the E.S.R. is related to the dental status in Table II. The association between the occurrence of a dental abscess and the elevation of the E.S.R. is suggested by the facts that the only two children with elevation of the E.S.R. during treatment had dental abscesses and that all the other four children with dental abscesses had a rebound, whereas in the other groups of children not more than half had a rebound.

TABLE II  
RELATIONSHIP BETWEEN DENTAL LESIONS AND  
COURSE OF ERYTHROCYTE SEDIMENTATION RATE

Dental Condition	Number of Cases	Number in which the E.S.R. failed to Settle	Number with Rebound
Minimal Caries . . . . .	11	0	6
Deep Cavities but No Dead Teeth			
Periodontal Condition Good . .	4	0	2
Non-vital or Loose Deciduous Teeth	Prophylactic extraction . .	4	0
	Developed abscess . .	6	2
	Others . . . . .	9	0

If we accept the premise of an association between the activated dental lesions and the raised E.S.R.,

then the response of the E.S.R. is greater than that observed in children without rheumatic fever. The possibility then arises that these children with rheumatic fever were exceptionally sensitive to even minimal stimuli. This suggestion would be compatible with the hypothesis that rheumatic fever is a manifestation of a tuberculin type of hypersensitivity to bacterial allergens (Long, 1954).

In the present small group of cases, over half the children had very carious and dead teeth; 40 per cent. of children with such a dental state can expect the activation of a dental abscess, and it is clearly necessary that they should receive very careful and thorough dental treatment. The timing of this treatment is probably best determined by the individual child's general condition and the facilities available. The need for careful management of children undergoing even minor surgery during or after cortisone therapy must always be remembered. The removal of non-vital and loose deciduous teeth early in the course of treatment with cortisone will prevent the development of dental lesions, but it will not abolish the occurrence of the rebound, which is due to multiple factors. A failure of the E.S.R. to settle and a rebound of the E.S.R. after stopping treatment should always lead to a careful examination of the mouth, particularly for the kind of dental condition described above.

### Summary

A study has been made of the dental state of 34 children with rheumatic fever receiving treatment with cortisone either alone or in combination with salicylates.

Nineteen of the 34 children had carious and dead teeth. Four of these had early dental treatment, but six of the other fifteen developed a dental abscess either during or within 2 weeks of stopping cortisone therapy.

The cortisone appeared to activate a pre-existing periodontal lesion. The abscesses which developed were remarkable for the very few symptoms which they caused.

The relationship between the dental abscess and the erythrocyte sedimentation rate is discussed. Whereas in normal children this is seldom appreciably elevated, it was raised in all the six children in this series when a dental abscess developed.

It is difficult to distinguish the relative importance of the various causes of raised erythrocyte sedimentation rates in children with rheumatic fever, but there did seem to be an association between the dental lesions and a raised erythrocyte sedimentation

rate. It is suggested that this may be due to the fact that children with rheumatic fever are particularly sensitive to even minimal stimuli affecting the erythrocyte sedimentation rate.

We are grateful to Prof. R. S. Illingworth, Professor of Child Health, and to Prof. G. L. Roberts, Director of Dental Studies, for allowing us to study children under their care, and for advice and criticism.

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### Activation des infections dentaires par la cortisone. Etudes des enfants atteints de rhumatisme articulaire aigu

#### RÉSUMÉ

On étudia l'état dentaire de 34 enfants atteints de rhumatisme articulaire aigu et traités par la cortisone seule ou bien associée aux salicylates.

Sur 34 enfants, 19 d'entre eux avaient des dents cariées ou mortes. Quatre d'entre eux avaient reçu un traitement dentaire antérieur, mais six sur les quinze restants ont développé un abcès dentaire soit pendant le traitement par la cortisone, soit au cours de deux semaines qui ont suivies son interruption.

La cortisone semblait activer une lésion périodontique préexistante. Les nouveaux abcès se caractérisaient par la rareté de symptômes.

On discute les rapports entre les abcès dentaires et la vitesse de sédimentation globulaire. Tandis que chez des enfants normaux elle est rarement trop élevée, chez les six enfants de cette série on a noté son augmentation dès la formation de l'abcès dentaire.

Il est difficile de déterminer l'importance relative de différentes causes de la vitesse de sédimentation globulaire élevée chez des enfants atteints de rhumatisme articulaire aigu, mais il semble bien qu'il y avait un rapport entre les lésions dentaires et la sédimentation plus rapide. Ceci pourrait être dû au fait que les enfants atteints de rhumatisme articulaire aigu sont particulièrement sensibles même à des stimulations minimes affectant les érythrocytes.

### Activación de infecciones dentales por la cortisona Estudios en niños con reumatismo poliarticular agudo

#### SUMARIO

Se estudió el estado de la dentadura en 34 niños con reumatismo poliarticular agudo, tratados con la cortisona sola o asociada a salicilatos.

De los 34 niños examinados, 19 tuvieron dientes cariados o muertos. Cuatro de estos obtuvieron tratamiento dental anterior, pero seis de los quince restantes formaron un absceso dental sea durante el tratamiento con la cortisona, sea dentro de 2 semanas de su interrupción.

La cortisona pareció activar una lesión periodóntica preexistente. Los abscesos nuevos se caracterizaron por pocos síntomas.

Se discuten las relaciones entre los abscesos dentales y la velocidad de sedimentación eritrocitaria. Mientras que en niños normales ésta se ve raramente muy elevada, en los seis niños de esta serie se notó su elevación con la formación del absceso dental.

Es difícil determinar la importancia relativa de las causas diferentes de la velocidad eritrocitaria elevada en niños con reumatismo poliarticular agudo, pero una relación entre las lesiones dentales y la sedimentación más rápida parece existir. Esto se puede deber al hecho de que niños con reumatismo poliarticular agudo acusan una sensibilidad particular hasta a estímulos mínimos que afectan los eritrocitos.

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## TUBERCULOUS RHEUMATISM

BY

JOAN M. BREMNER

University of Leeds and Regional Rheumatism Centre, Harrogate, Yorks

The problem of "tuberculous rheumatism" has been studied with a varying amount of interest during the past 60 years, mainly in France, though some work has been done in Great Britain and the United States. Layani, Durupt, and Chaouat (1956) reviewed the subject and tried to define the syndrome more exactly by using a test specific for tuberculosis, the tuberculin test. The results were compared with those of a similar injection of non-specific foreign protein, in patients with tuberculosis associated with past or present articular lesions, and in others with rheumatoid arthritis. A similar attempt at definition, using a different approach, the Rose-Waaler (D.A.T.) test for rheumatoid arthritis, has been made in the three cases reported below.

### Case Reports

**\*Case 1, a married woman, aged 49 years,** had rheumatoid arthritis which started with pain in the neck and hands at the age of 32 years, followed by gradual involvement of most joints; after some years and following several falls, the left knee worsened considerably, though there was no constitutional upset or loss of weight.

On admission the patient complained chiefly of this joint, which was swollen and tender with very limited movement; most of the other joints were affected and there was ulnar deviation of the right hand.

**Laboratory Findings.**—Haemoglobin 63 per cent., white blood cells 4,500 c.mm., polymorphs 58 per cent., lymphocytes 39 per cent.

Blood sedimentation rate 43 mm./1 hr.

X ray of the left knee showed osteoporosis and loss of joint space.

The Rose-Waaler test was positive 1 : 256 in 1957, i.e. at a late stage of the disease.

**Progress.**—Though the general condition and other joints improved with treatment, the left knee remained very painful. The patient was given two intra-articular injections of hydrocortisone with temporary slight relief, but when a third injection was attempted, some synovial fluid was aspirated and found to be turbid. Tubercle bacilli were found in the fluid both microscopically and on culture. No other form of tuberculosis was found, and arthrodesis of the knee was performed.

After this, the patient's condition improved considerably for about 2 years, but she then relapsed with

reactivation of arthritis in several joints and has recently died from an intercurrent pyelo-nephritis and broncho-pneumonia.

**Post-mortem Examination.**—No other evidence of tuberculosis was found.

**Case 2, a married woman aged 47 years,** the sister of Case 1, had rheumatoid arthritis starting at the age of 27 years with pain and swelling of fingers. She was given one course of gold, with temporary improvement. Shortly afterwards the shoulders and knees also became painful, but settled after a second course of gold, apart from slight swelling of the hands and intermittent pain in the left arm, without constitutional upset or loss of weight. 3 years later, she began to suffer increasing pain in the left shoulder, which became swollen and finally broke down with sinus formation. The lesion was tuberculous and the joint was arthrodesed in 1944. No other tuberculous focus was found and the patient has remained well ever since apart from slight swelling and deformity of the fingers, tenderness of the right second proximal interphalangeal joint, and some pain in the hands after extra work.

The Rose-Waaler test was positive 1 : 32 in 1957, 16 years after the acute phase.

**Case 3, an unmarried woman, aged 43 years,** had rheumatoid arthritis starting at the age of 39 years with pain in the feet. Involvement of the hands followed a few months later, with some constitutional upset but no loss of weight.

On admission, the patient complained of pain in most joints, and there was spindling of the fingers, ulnar deviation of the right hand, and a nodule on the right elbow.

**Laboratory Findings.**—Haemoglobin 46 per cent., white blood cells 12,000 c.mm., polymorphs 96 per cent., lymphocytes 7 per cent.

Blood sedimentation rate 53 mm./1 hr.

The Rose-Waaler test was positive 1 : 64 in 1957, 2 years after the clinical remission.

**Progress.**—Shortly after admission she developed a right pleural effusion which proved to be tuberculous, with involvement of the underlying lung. She was transferred to a sanatorium where her progress was stormy at first, but improved after surgery.

She is now working part-time and reports that her joints remained painful until after her operation 2 years ago, but that now all swelling has gone, her hands and feet are normal, and the nodule on her elbow has disappeared.

\* This case was reported to a meeting of the Heberden Society at Harrogate in May, 1954.



### Discussion

About 60 years ago there was much discussion in the European medical literature regarding the possibility of a tuberculous aetiology in certain cases of chronic polyarthritis, which, clinically and radiologically, were indistinguishable from rheumatoid arthritis. A small proportion of these cases were said to develop a typical tuberculous arthritis of one joint at some point in their evolution.

The principal protagonist of this theory was Poncet, who between 1897 and 1909 described the different clinical pictures which he considered might be found in tuberculous rheumatism (Poncet and Leriche, 1909). These included transient arthralgias and acute or subacute rheumatism, which might be primary when they preceded other manifestations of tuberculosis, or secondary when they supervened during the course of visceral tuberculosis. The acute form was apparently indistinguishable from rheumatic fever, while the subacute form resembled rheumatoid arthritis. Poncet thought that the subacute primary form was the commonest, and that in its course the polyarthritis might slowly localize to one joint which later became the site of a typical tuberculous arthritis. He claimed that in such cases injections of tuberculin produced a focal reaction in affected joints and that, on occasion, Koch's bacilli had been cultured from synovial fluid. His views were supported by Thomson (1910) and Raw (1914), but on the whole were not accepted in Great Britain or America.

Interest in the concept faded, but was revived in 1925, mainly through bacteriological work in Paris, where workers claimed to have cultured Koch's bacilli from blood, synovial fluid, and biopsy material from certain patients suffering from apparently typical rheumatoid arthritis. The subject was fully discussed at the III International Congress in 1932, when Besançon, summarizing the findings, concluded that a tuberculous aetiology for the rheumatic process should only be admitted when either the articular and visceral manifestations evolved together, or the rheumatic lesions, after a long or short course, ended by accompanying a florid tuberculous arthritis.

Brav and Hench (1934), in a comprehensive review of the subject, felt that there was as yet no incontrovertible proof of the existence of the syndrome of tuberculous rheumatism. They thought that the presence of Koch's bacilli in a joint, or the development of a typical tuberculous arthritis, might indicate a super-infection of one joint with tubercle, just as easily as that the whole arthritic process was tuberculous.

However, Forestier (1935) considered that there

were grounds for believing that tuberculosis was a prominent factor in the aetiology of certain cases of rheumatoid arthritis.

Collins and Cameron (1936), reporting twelve cases of arthritis, in eight of whom visceral tuberculosis was proved, though not denying the possible influence of associated visceral tuberculosis on the production and course of the articular disease, preferred not to use the term "tuberculous rheumatism" for two reasons: because every case pursued a course consistent with non-specific arthritis, and because immobilization treatment, adopted on the suspicion that the condition was tuberculous, proved totally unsuitable in each case. They pointed out that the two diseases occurred but rarely in one patient, and that only two patients with true rheumatoid arthritis had been seen among 2,179 tuberculous patients. They quoted Pemberton (1935), who had reported eleven cases of rheumatoid arthritis among 4,499 cases of pulmonary tuberculosis, and Brav and Hench's figure of eight cases of tuberculosis among 250 rheumatoid arthritics. They felt that such figures refuted the suggestion that tuberculosis was a frequent or important factor in the aetiology of rheumatoid arthritis.

Copeman (1936), discussing twelve cases of polyarthritis in whom evidence of tuberculosis, including a positive blood culture by Löwenstein's method, was found, thought that tuberculosis should be considered in the aetiology of any obscure case of rheumatoid arthritis. More recently, Dalgleish (1952) reported a case of polyarthritis occurring in a young girl, which quickly resolved but was followed by an arthritis of the hip which was clinically and radiologically typical of tuberculosis. No primary focus was discovered and the author felt that the polyarthritis was a sensitization phenomenon to the tubercle bacillus, which later infected the hip joint.

Layani and others (1955), in a careful study of the problem, concluded that the only form of articular disease that could truly be called "tuberculous rheumatism" was a transient acute or subacute polyarthritis occurring during the course of a frank or hidden tuberculous infection. This conclusion was not accepted by Weil (1955), who was convinced that tuberculosis would cause a chronic polyarthritis.

Short, Bauer, and Reynolds (1957), in their long-term study of 293 patients with rheumatoid arthritis, stated that pulmonary tuberculosis was present in five on admission and that four other patients developed it during the study. Two patients in the series developed a tuberculous arthritis; both these patients had typical rheumatoid arthritis, one with definitive histology in a subcutaneous nodule. One

later developed a tuberculous arthritis, the other glandular, pulmonary, and articular, tuberculosis. The authors felt that in these two patients coincidental tuberculosis and rheumatoid arthritis were present, but they thought that the possibility of a true tuberculous polyarthritis had to be considered in such cases.

The fact that the Rose-Waaler test (D.A.T.) was positive in all three cases reported in this paper (at a late stage in the disease in Case 1, 16 years after the acute phase in Case 2, and 2 years after clinical remission in Case 3) suggests that, in these cases too, tuberculosis and rheumatoid arthritis were coincidental.

Recent work by Lawrence and Ball (1958) among the relatives of rheumatoid arthritics, showed that 20 per cent. of relatives of sero-positive cases were also sero-positive, though they might be symptom-free. The fact that Case 2 is the sister of Case 1, might thus account for her positive result, which is in low titre; on the other hand, she had a definite polyarthritis which was fairly acute for over a year, and she still has residual swelling and minimal pain in her fingers.

On the whole, it is felt that, though these cases would fit into Poncet's description of subacute primary and secondary tuberculous rheumatism and would fulfil the stricter criteria laid down by Besançon (1932), the finding of a positive Rose-Waaler test (D.A.T.) in all three gives further support to the narrower definition of "tuberculous rheumatism" advanced by Layani and others (1955).

#### Summary

The concept of "tuberculous rheumatism" and its evolution is described.

Three cases are reported which fulfil various criteria laid down for tuberculous rheumatism.

The finding of a positive Rose-Waaler test (differential agglutination test) in all three cases, suggests that, in these patients, tuberculosis and rheumatoid arthritis are coincidental.

It is felt that this finding gives support to the narrower definition of tuberculous rheumatism which has been advanced recently.

My thanks are due to Prof. S. J. Hartfall for permission to investigate these cases under his care, to Dr. V. Wright, who kindly did the Rose-Waaler tests (D.A.T.) (using the method of Greenbury), and to Dr. McMillan, who gave me information on the progress of Case 3.

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#### Rhumatisme tuberculeux

##### RÉSUMÉ

On décrit la conception du "rhumatisme tuberculeux" et son évolution.

On relate trois cas correspondant à de différents critères proposés pour le rhumatisme tuberculeux.

La réaction de Rose-Waaler (agglutination différentielle) positive dans les trois cas suggère que chez ces malades la tuberculose et l'arthrite rhumatismale coïncidaient.

On pense que ces résultats supportent une définition du rhumatisme tuberculeux plus étroite que celle proposée récemment.

#### Reumatismo tuberculoso

##### SUMARIO

Se describe el concepto de "reumatismo tuberculoso" y su evolución.

Se relatan tres casos que responden a los varios criterios propuestos para el reumatismo tuberculoso.

La reacción de Rose-Waaler (aglutinación diferencial) positiva en los tres casos sugiere que en estos casos la tuberculosis y la artritis reumatoide fueron coincidentes.

Se cree que este resultado sostiene una definición de reumatismo tuberculoso más estrecha que la propuesta recientemente.

## BOOK REVIEWS

**Bréviaire de rhumatologie à l'usage du praticien.** Par les Médecins du Service de Rhumatologie du Centre Viggo-Petersen et S. de Sèze. 1958. Pp. 370, 178 figs. Expansion Scientifique, Paris. (4,000 Fr. frs.)

This synopsis is intended for the general practitioner who is faced with a rheumatological problem. Consequently, the authors have omitted non-essentials, as far as possible, and concentrated on the two indispensables—diagnosis and treatment. Information is imparted by means of question and answer, and by looking up the relevant chapter the reader may find the solution to his problem. From this it must be concluded that the authors have compiled a variation of "Any Questions?"; the text is well illustrated with photographs, diagrams, and x-ray films, and abounds in useful information and clinical observations which merit respect, though not necessarily always full agreement. For example, it may not be realized that partial or complete rupture of the supraspinatus tendon is found in 10 to 15 per cent. of all autopsies; that this incidence rises to 70 per cent. in those who have passed the psalmist's span of life; that fraying of the long head of biceps is present in 20 to 50 per cent. of persons over the age of 70, and that correlation with symptoms during life indicates that such lesions can be silent or latent; that phenylbutazone is the drug of choice in ankylosing spondylitis and that its administration in the early stages will arrest the disease—and so on and so forth. Incidentally, the term "ankylosing spondylitis" is once more under attack by the authors on the grounds that it does not incorporate the salient feature of the disease (involvement of the sacro-iliac joints), and arouses despair in the patient by its suggestion of inevitable invalidism. They suggest instead the use of the term *pelvi-spondylite rhumatismale*—which all goes to show that the practice of pouring new wine into old bottles has lost none of its attractions.

The quality of printing and of paper is above reproach. There are two special features which are worthy of mention—a separate chapter on bone pathology, which

is of great interest, and an ample supplement in which the pharmaceutical houses and purveyors of orthopaedic appliances have found full scope for their talents. A table of contents is provided but no index. The volume will prove to be of interest both to general practitioners and to rheumatologists, but its price is rather high by British standards.

DAVID PREISKEL.

**Manual of Rheumatology.** By J. Houli. 1958. Pp. 157, 57 figs. Livraria Athenell S.A., Rio de Janeiro, Brazil.

This book may be described as a simple, systematic study of the rheumatic diseases. For the specialist everything in it is familiar, but for the student and the general practitioner it offers a comprehensive survey of the "rheumatic problem". The material, especially the section on treatment, is well up-to-date. There are 57 useful photographic reproductions and some interesting statistical data. Although rheumatism, in its various forms, is supposed to be commoner in the temperate climates, it is quite obvious from the text that it presents a considerable problem in South America.

PAUL B. WOOLLEY.

**The Synovial Fluid.** By J. Houli. 1958. Pp. 204, illus. Livraria Athenell, S.A., Rio de Janeiro, Brazil.

It is difficult to imagine a more specialized text than this one—187 pages devoted almost solely to the study of synovial fluid. Needless to say this book has been written for the specialist and it contains all, and even more, that he need ever know about the lubricating liquid. The author believes that joint aspiration should be carried out as a routine and the fluid examined in the same manner as a haematologist would do a blood-count. Samplings of fluid can give some indication as to the value of any treatment being carried out.

There are ample illustrations and tables and the bibliography can be described as complete.

PAUL B. WOOLLEY.

## CANADIAN RHEUMATISM ASSOCIATION

### *Annual Meeting, 1958*

At the annual meeting of the Canadian Rheumatism Association, held at Vancouver, B.C., the scientific session comprised eleven papers dealing with original reports, reviews, and clinical observations.

Dr. Russel L. Cecil and Dr. A. Almon Fletcher, and Mr. J. A. Gairdner, a Toronto philanthropist, were elected honorary members of the Association.

Dr. John F. L. Woodbury (*Halifax*) is the new President, and other incoming members of the executive committee are Dr. J. Bruce Frain, first vice-president; Dr. Metro Ogrzylo, second vice-president; Dr. de Guise Vaillancourt, secretary; Dr. John R. Martin, treasurer; Dr. Joseph A. Blais and Dr. H. Garfield Kelly.

The Canadian Rheumatism Association has



decided to accept the invitation of the President of the Heberden Society to participate with the British group in a joint scientific session to be held at Buxton, England, in 1959. The annual business

meeting will, however, be held in June, 1959, in Washington, D.C., at the time of the Second Congress of the Pan-American League against Rheumatism.

## GAIRDNER FOUNDATION

The first international awards in arthritis and heart disease, totalling \$40,000, have been announced, and medical scientists from England, the U.S.A., and Canada are included among the seven recipients.

*Gairdner Foundation Award of Merit* to Dr. Alfred Blalock and Dr. Helen B. Taussig (Johns Hopkins University, Baltimore, Md) for their initial development of what is known to the public as the "blue-baby operation".

*Gairdner Foundation Annual Awards* to Dr. Harry M. Rose and Dr. Charles Ragan (New York City) for their discovery of the first practical laboratory test for the diagnosis of rheumatoid arthritis; to Prof. W. D. M. Paton and Prof. Eleanor Zaimis (London, England) for their discovery of the first drugs to be proven practical and effective in the treatment of high blood pressure; to Dr. W. G. Bigelow (Toronto, Ontario, Canada) for his development of the technique of hypothermia, or the "deep-freeze" operation for heart surgery.

## II. PAN-AMERICAN CONGRESS ON RHEUMATIC DISEASES

*Washington, D.C., and Bethesda, Md., U.S.A., 1959*

In the years 1940 to 1942, when Dr. Ralph Pemberton, then President of the International League against Rheumatism, was travelling in South America, and Dr. Anibal Ruiz-Moreno, President of the Argentine Society of Rheumatology, was visiting rheumatism centres in the United States, Dr. Ruiz-Moreno conceived the idea of organizing the rheumatism societies of the two Americas into a Pan-American League. His idea was greeted with enthusiasm, and by June, 1944, the organization was completed.

The countries now belonging to the Pan-American League against Rheumatism are: Argentina, Brazil, Canada, Chile, Cuba, Mexico, Paraguay, Peru, Uruguay, U.S.A., and Venezuela.

In 1953, at the time of the X International Congress on Rheumatic Diseases, preparations were begun for the First Pan-American Congress, which was held in Brazil in 1955 and was attended by 239 representatives of sixteen countries. The scientific sessions were a signal success and the social aspects of the programme were so delightful that all participants received a deep impression of the polished culture and warm hospitality of their Brazilian hosts.

### *Arrangements for the Second Congress*

The Pan-American Committee and local members of the American Rheumatism Association are the

organizers of the II Pan-American Congress, which will open at Washington, D.C., on June 2, 1959, at the Pan-American Union, and will be held in conjunction with the 23rd Annual Meeting of the American Rheumatism Association.

On June 3, our guests will be entertained at private dinner parties in the homes of our Washington hosts. On June 4, a reception will be held at the Capitol, after which members will be able to watch a baseball match or attend a horse race meeting. The official banquet preceded by a cocktail party will be held on June 5 at the Mayflower Hotel. The formal closing ceremony will take place on June 6. Many special events are also being planned for members' ladies and families, and there will be ample time for sightseeing in and around historic Washington.

The Mayflower Hotel, 1127 Connecticut Avenue, N.W., Washington, D.C., will be official headquarters for the Congress. Registration will be carried out here for the scientific sessions and social events. An Information Bureau staffed with interpreters will be maintained at all times at the hotel and also at the Clinical Centre, National Institute of Health, Bethesda, Maryland, where some of the scientific sessions will be held.

The official hotels for the Congress are:

MAYFLOWER HOTEL (Headquarters),  
1127 Connecticut Avenue, N.W.

BLACKSTONE HOTEL,  
1016 17th Street, N.W.

BURLINGTON HOTEL,  
1120 Vermont Avenue, N.W.

YOUNG MEN'S CHRISTIAN ASSOCIATION (Men only)  
1736 G. Street, N.W.



Application forms for registration and hotel reservations may be obtained from and should be returned *not later than March 1, 1959*, to the Secretary-General:

Dr. Richard T. Smith,  
West Point,  
Pennsylvania, U.S.A.

The fee for registration for each individual attending (congressists, wives, and families) will be \$15.00 (U.S. currency); this includes registration, programme, admission to the scientific sessions and exhibits, and to all official social events including the formal cocktail party and banquet.

The official languages will be English, Portuguese, and Spanish. Simultaneous translation will be undertaken for all plenary sessions.

The American Express Company will act as authorized agent in all matters regarding transportation, hotel reservations, foreign exchange, etc.

Members of the Medical Corps, Army, Navy, Public Health Service, Air Force, and Veterans Service of any of the participating countries, and also medical students, interns, and residents of hospitals of the Americas are invited to attend the scientific sessions free of charge.

#### *Submission of Scientific Papers*

Papers on both clinical and laboratory aspects of rheumatic diseases are invited, and titles and abstracts for consideration for presentation at the Congress should be submitted not later than February 1, 1959, to the Chairman of the Programme Committee:

Dr. John Vaughan,  
University of Rochester School of Medicine,  
260 Crittenden Boulevard,  
Rochester, New York, U.S.A.

Abstracts may be submitted in the author's native language but must be accompanied by an English translation; they should be limited to 300 words and ten copies are required.

The Programme Committee wishes to emphasize that those Abstracts containing factual material and definite conclusions will be given preference.

## HEBERDEN SOCIETY

**Clinical Meeting.\***—At a meeting held on October 11, 1958, at the Stoke Mandeville Hospital, Aylesbury, Bucks, cases were demonstrated by Dr. A. G. S. Hill, Dr. M. S. Good, Dr. D. S. Wilkinson, and Mr. G. Black.

Clinical and scientific demonstrations were given by Prof. S. J. Hartfall, Dr. G. N. Chandler, Dr. M. S. Good, Dr. D. G. Scott, and Dr. V. Wright.

The following papers were delivered:

Dr. M. S. Good (*Aylesbury*): Temporal or giant cell arteritis.

Dr. A. R. Horler (introduced) and Dr. M. Thompson (*Newcastle-upon-Tyne*): Pleural effusion in rheumatoid arthritis.

Dr. L. J. Barford (*London*): A case of rheumatoid arthritis with recurring pericarditis, L.E. cells, and multiple basal lung nodules containing tubercle bacilli.

Dr. A. G. S. Hill and Dr. D. L. Greenbury (*Aylesbury*): Marrow iron in rheumatoid arthritis.

Dr. W. R. M. Alexander (*Edinburgh*): Elution of rheumatoid agglutinating factor from sensitized Bentonite.

Dr. J. F. Buchan (*London*): Chloroquine in rheumatoid arthritis.

A discussion of clinical experience with Triamcinolone and Dexamethasone was opened by Dr. H. F. West (*Sheffield*).

The Annual General Meeting is to be held on December 5 and 6, 1958, at the Wellcome Foundation, London, N.W.1. The Heberden Oration for 1958 will be delivered by Dr. Charles Ragan on December 5, at 5 p.m., at the Wellcome Foundation. The Annual Dinner will take place on December 5 at the Apothecaries' Hall, Blackfriars, E.C.4.

\* A full account of this meeting will appear in the *Annals of the Rheumatic Diseases* in March, 1959.

## ABSTRACTS

This section of the ANNALS is published in collaboration with the two abstracting Journals, ABSTRACTS OF WORLD MEDICINE, and OPHTHALMIC LITERATURE, published by the British Medical Association.

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Pararheumatic (Collagen) Diseases; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with research into the scope and modus operandi of steroid therapy.

### Acute Rheumatism

**Psychosomatic Study of Eight Children with Sydenham's Chorea.** CHAPMAN, A. H., PILKEY, L., and GIBBONS, M.J. (1958). *Pediatrics*, 21, 582. 12 refs.

The results are reported of a psychiatric study of eight patients with Sydenham's chorea admitted to the Children's Mercy Hospital, Kansas City, over a period of 18 months. The personality of the patients was marked by passivity, with inability to express anger or assertion or to accept with equanimity the hostility of others. There was withdrawal from interpersonal relationships, varying from that of extreme shyness to schizophrenia, and much basic anxiety and suppressed anger. Depression and phobic and obsessive symptoms were noted in some of the children, one of whom could be assertive and angry, but later experienced strong feelings of guilt as a consequence. Two were definitely schizophrenic and five were schizoid; seven of the patients were the eldest or second eldest in the family. None of the patients' siblings had suffered from Sydenham's chorea. The sex incidence was equal and the ages ranged from 7 to 16 years. No evidence of rheumatic fever was found in three cases, and in one other it was indefinite. In five cases the onset of chorea closely followed severe emotional stress, while in two others the correlation with such stress was equivocal. Brief histories of all eight cases are presented.

G. de M. Rudolf.

**Prevention of Rheumatic Fever.** WOOD, H. F. (1958). *Amer. J. Cardiol.*, 1, 456. 1 fig., 22 refs.

The author presents an interim report of an experiment begun in May, 1954, at Irvington House, Irvington-on-Hudson, under the auspices of New York University College of Medicine, in an attempt to determine the most effective form of prophylaxis against rheumatic fever. This 5-year study is being carried out on 407 children with unequivocal histories of rheumatic fever who were allotted by random selection to one of three treatment groups given respectively:

- (1) 1 g. sulphadiazine daily in a single dose,
- (2) buffered potassium benzylpenicillin, 200,000

units by mouth in a single dose half an hour before breakfast,

- (3) 1.2 mega units benzathine penicillin intramuscularly once a month.

Each patient is seen monthly, when in addition to a history and physical examination a throat swab is taken for culture and blood for streptococcal antibody determinations.

At the end of the third year the results for 890 patient-years are here analysed. A total of 145 streptococcal infections have occurred in the 407 patients, 67 in Group 1, 57 in Group 2, and 21 in Group 3. A rheumatic relapse occurred in six (9 per cent.) infections in Group 1, in twelve (21 per cent.) in Group 2, and in one (5 per cent.) in Group 3.

The results so far show that fewer relapses occurred in patients in Group 1 (sulphadiazine) than in Group 2; while the difference between these two groups is not yet statistically significant because of the relatively small numbers, the findings do suggest that the dosage of oral penicillin is inadequate and that the dose recommended by the American Heart Association of 250,000 units penicillin twice a day by mouth might be more effective.

It is clear from these studies up to date that the third method of prophylaxis—that is, monthly intramuscular injections of benzathine penicillin—has proved the most effective. The study has also shown that the incidence of streptococcal infections is much higher in children in the younger age groups, the incidences being 27, 14, and 2 per cent. in the age groups 6-10, 11-15, and over 15 respectively.

C. Bruce Perry.

**A Study of the Iron Content of the Bone Marrow during the Course of Rheumatic Fever in Children.** (Étude du fer médullaire au cours du rhumatisme articulaire aigu de l'enfant.) BERNHEIM, M., MOURIQUAND, C., and GERMAIN, D. (1958). *Sem. Hôp. Paris*, 34, 1813. 5 figs, 15 refs.

Hypochromic anaemia is a frequent concomitant of rheumatic fever and examination of the bone marrow reveals a decrease in the number of erythroblasts in nearly 50 per cent. of cases. The authors, working at the

Hôpital Edouard-Herriot, Lyons, have examined the iron content of 119 specimens of bone marrow from 87 children aged 5 to 15 years with rheumatic fever, using the Prussian blue method, and here present the conclusions drawn from these investigations.

The cytoplasm of erythroblasts contains granular, iron-containing elements called sideroblasts, while extra-erythroblastic iron, when present, is found in diffuse masses in the cytoplasm of the reticular cells of the bone marrow, where its presence is more difficult to determine precisely. In the healthy child extra-erythroblastic iron is found in minimal quantities, but in the acute stage of rheumatic fever there is a fall in the number of sideroblasts and a marked rise in the quantity of extra-erythroblastic iron, which tends to congregate in the vicinity of the erythroblasts. Such changes are most marked during the first 10 days after the onset of joint involvement, and the appearance of the bone marrow tends to return to normal with clinical improvement. The findings in this study suggest that iron accumulates in the cells of the reticulo-endothelial system in the inflammatory stage, being unable to penetrate to the interior of the erythroblasts. Rapid suppression of the inflammatory process, as by steroid therapy, leads to a return of the distribution of iron in the bone marrow to normal.

D. Preiskel.

**Decline of Rheumatic Fever. Recurrence Rates of Rheumatic Fever among 782 Children for 21 Consecutive Calendar Years (1936-1956).** WILSON, M. G., WAN NGO LIM, and BIRCH, A. MCA. (1958). *J. chron. Dis.*, 7, 183. 6 figs, 18 refs.

Reports from various sources have suggested a decrease in the incidence of, and morbidity and mortality from, rheumatic fever during the past 20 years, antedating in onset the introduction of antibiotics, and in this paper from the New York Hospital changes in the recurrence rate of rheumatic fever during the years 1936-56 have been studied. From the consecutive records of 782 children (370 male and 412 female) born since 1916 who had attended the Cardiac Rheumatic Clinic and had been under satisfactory supervision, the age-adjusted annual recurrence rates of rheumatic fever for the ages 2 to 20 years were calculated.

There was a total of 613 recurrences and, apart from minor fluctuations, there was a significant progressive decline in the annual recurrence rate, with a slope of -0.4 per cent. per year, which was not seen in the preceding 12 years. The mean annual recurrence rate among those patients experiencing a recurrence within 2 years of the primary attack was three times as great as that among patients in whom there was a longer interval between attack and recurrence, although both groups showed a significant decline in recurrence rate during the period. In almost every age group the age-specific recurrence rate for the period 1916-43 was higher than that for 1944-56. While the start of the decline in the recurrence rates of rheumatic fever antedated the antibiotic era, it coincided with a progressive improvement in the standard of living in New York City since 1936, as reflected in the socio-economic composition of the patients attending the clinic.

B. M. Ansell.

**Tissue Culture Studies of Cellular Hypersensitivity in Rheumatic Fever. I. The Response of Human White Blood Cells to Streptococci and to Crude Filtrates of Streptococcal Cultures.** FLORIO, L., WEISS, G., and LEWIS, G. K. (1958). *J. Immunol.*, 80, 12. 5 figs, 38 refs.

**II. The Response of Fibroblasts from Human Skin and Heart to Disintegrated Streptococci and to Crude Filtrates of Streptococcal Cultures.** WEISS, G., FLORIO, L., and LEWIS, G. K. (1958). *J. Immunol.*, 80, 26. 2 refs.

**III. A Re-examination of Tuberculin Hypersensitivity in Tissue Culture by a Study of the Response to Old Tuberculin of Human White Blood Cells and Fibroblasts from Human and Guinea-Pig Skin.** FLORIO, L., LEWIS, G. K., WEISS, G., and OLSON, H. (1958). *J. Immunol.*, 80, 32. 3 figs, 8 refs.

In these three studies, reported from the University of Colorado, Denver, tissue culture techniques were used to test the theory that rheumatic fever is associated with delayed hypersensitivity to streptococcal products of the tuberculin type. In the first paper the literature on tuberculin tissue responses and streptococcal tissue responses is first reviewed, and the methods of study are described [for details of which the original paper must be read]. Essentially they consisted in observing the behaviour of leucocytes from healthy and rheumatic individuals while in contact with pooled normal and rheumatic sera, with and without the addition of streptococcal filtrate or disintegrated streptococci, the criteria of behaviour being the migration and spindle transformation of the leucocytes. The results showed such great variability, however, that it was impossible to distinguish serum from cases of rheumatic fever from normal serum. Although there was some depression of cellular activity in rheumatic-fever leucocytes exposed to streptococcal antigen, there was no consistent or statistically significant difference.

In the second study the authors observed in a similar way the growth of fibroblasts from skin and from heart, for which material from 43 skin biopsies and fifteen auricular tips were examined. Fibroblastic growth in material from rheumatic individuals was inhibited by a lower concentration of streptococcal filtrate and disintegrated streptococci than that necessary for inhibition of normal fibroblasts, but there was considerable overlap of the results so that individual responses could not be evaluated. There was no difference between the reactions of fibroblasts from skin and from heart and no effect was observed if rheumatic serum was used rather than normal serum.

In the third study, employing similar techniques, the response of leucocytes and fibroblasts from healthy and from tuberculous subjects to various concentrations of old tuberculin was observed. No difference was found. However, the growth of skin fibroblasts from five guinea-pigs was inhibited by significantly smaller concentrations of old tuberculin after sensitization than before it. Even here, however, variability was so great that it was not possible always to distinguish sensitized from a non-sensitized animal.



The authors conclude that cellular sensitivity in man, in so far as the above results support such a hypothesis, is more evident in rheumatic fever than in tuberculosis.

E. G. L. Bywaters.

**Practical Application and Results of the Prolonged Systematic Prevention of Recurrences of Rheumatic Fever with Continuous Penicillin Treatment.** (Remarques sur l'application pratique et les résultats de la prévention systématique prolongée des rechutes du rhumatisme articulaire aiguë par la pénicilliothérapie continue) KAPLAN, M., and FISCHGRUND, A. (1958). *Pédiatrie*, 13, 35.

During the period 1951-56 inclusive, 89 patients were admitted to the Hôpital Hérold, Paris, with acute rheumatism, 66 of whom remained under regular observation after their discharge. Systematic prophylaxis against relapses was instituted in 1955, since when forty of the 66 patients, including most of those admitted since 1954 and ten of the 25 admitted before that date, have received this treatment. The method adopted in 42 cases was to give an intramuscular injection of 600,000 units of benzathine penicillin every 10 days, while five patients were treated with penicillin daily by mouth and one received penicillin by mouth at first, but subsequently by injection.

No case of relapse has occurred during continued prophylactic treatment, whereas of those patients who were admitted before 1955 (totalling 56, including those not kept under observation), seventeen relapsed, one twice and another three times. Of the twenty relapses, nine occurred in the first 12 months after the initial attack, fifteen in the first 18 months, and eighteen in the first 2 years. Some of these patients had received discontinuous penicillin prophylaxis since their first attack, but none of the eleven who have been given continuous treatment since relapsing have suffered a further relapse.

A curious fact is that none of the eight patients admitted to hospital since 1955, who, for various reasons, were not given continuous prophylaxis, has relapsed. It is suggested that this might be due to the fact that the parents had been made aware of the risk of relapse, and that in consequence any fever, sore throat, or upper respiratory infection has been energetically treated with penicillin.

C. Bruce Perry.

**Comparative Study of Treatment with Hormones, Salicylates, and Phenylbutazone in 631 Attacks of Rheumatic Fever observed in 4 Years.** (Étude comparée des traitements hormonaux, salicylés, et par la phénylbutazone, d'après 631 crises rhumatismales aiguës observées en 4 ans.) CHEVALLIER, J. (1958). *Rev. Rhum.*, 25, 1. 8 figs, 6 refs.

This paper summarizes the results of an investigation carried out at thirteen French medical centres during the 4-year period 1953-56 into the treatment and subsequent course of 631 attacks of rheumatic fever, of which 497 occurred in children. Three types of treatment were used:

- (1) aspirin or sodium salicylate in doses of 100 to 150 mg. per kg. body weight, according to age;

- (2) corticosteroids, usually as prednisone, in a daily dose of 30 to 40 mg. for periods varying from 3 to 7 weeks;

- (3) phenylbutazone in a dosage of 10 mg. per kg. body weight daily.

In addition, all the patients received intramuscularly 1,000,000 units benzylpenicillin daily for at least 7 days. In 68 per cent. of the cases treatment was started within 2 weeks of the onset of the attack.

Joint swellings disappeared in patients in all three groups in from 1 to 4 days. The mean fall in temperature in the febrile cases was similar in all groups, but was slightly more rapid in those given corticosteroids. The erythrocyte sedimentation rate (E.S.R.; Westergren method) fell more slowly in the group treated with phenylbutazone, levels in this group of 20 mm. or more after one hour being maintained for over 6 weeks. The plasma fibrinogen level fell most rapidly in the group treated with corticoids, and this was a factor in the rapid fall of the E.S.R. As was anticipated, the cases treated with corticosteroids did not show the same rapid fall in the leucocyte count as did the other two groups. Leucopenia occurred in a few cases treated with phenylbutazone, but in no case was this severe. The anti-streptolysin-O titre showed variable changes in all groups. The "rebound phenomenon" following cessation of treatment occurred less frequently in the later years of the study when the dose of prednisone was more gradually tapered off than had been the practice earlier, but in half the cases treated with salicylates and two-thirds of those given corticosteroids there was a temporary rise in the E.S.R. when treatment ceased. No new cardiac murmurs were discovered during this period.

An analysis of cardiac abnormalities is presented [with the aid of a number of somewhat complicated tables], but the general conclusion is that murmurs appearing during treatment were evenly distributed among all three groups. The majority of cases in which murmurs were present at the onset were treated with corticoids or phenylbutazone, but it was only in the former group that harsh systolic or diastolic murmurs disappeared during treatment. There were fourteen cases of severe carditis, with four deaths. The introduction of penicillin therapy had no effect on the incidence of carditis. The complications observed were those commonly known to be associated with the drugs used. The author's general impression is that the best over-all results were obtained with prednisone, the frequency of the toxic reactions caused by phenylbutazone weighing against the otherwise excellent results obtained with this drug.

H. F. Reichenfeld.

**Prevention of Rheumatic Fever and Rheumatic Heart Disease: a Brief Historical Review and a Preliminary Report of Three Controlled Studies.** MASSEL, B. F., FYLER, D. C., HAZEL, M. M., MAUTNER, H., KAPLAN, M. H., STANCER, S. L., MILLER, J. M., GOEBEL, R., and BRODIE, S. (1957). *Bull. St. Francis Hosp. (Roslyn)*, 14, 1. 5 figs, 32 refs.

In this series of reports from the House of the Good Samaritan and Harvard Medical School, Boston, the



authors briefly review the development of rheumatic fever prophylaxis and present preliminary clinical studies of the efficacy of different schemes of penicillin administration, this last being assessed from the results of over 1,000 biological assays of serum penicillin levels.

It was found that buffered benzylpenicillin was better absorbed from the gastro-intestinal tract than benzathine penicillin, and that its absorption rate was not related to meals. Phenoxymethylpenicillin was absorbed about twice as well as buffered benzylpenicillin. These findings were confirmed in a controlled study of the effect of penicillin prophylaxis on the incidence of  $\beta$ -haemolytic streptococcal infection in the throats of 114 children. Buffered benzylpenicillin in a dosage of 200,000 units twice daily by mouth was more effective in reducing the incidence of clinical infections due to Group-A streptococci than infections causing a rise in antistreptolysin-O titre. The injection of 1.2 million units benzathine penicillin at intervals of one month was consistently more effective than oral administration in reducing the incidence of any type of Group-A streptococcal infection; this increased efficacy, however, was somewhat offset by the occurrence of reactions, including pain at the site of injection.

The authors conclude that penicillin is effective in reducing the incidence of recurrences of rheumatic fever, although the preparations now being used could be improved upon. At present, oral administration of phenoxymethylpenicillin or larger doses of buffered benzylpenicillin is probably adequate and approaches the effect of intramuscular injection of benzathine penicillin.

J. Warwick Buckler.

**Streptococcal Disease and Rheumatic Fever in Air Force Recruits. I. Epidemiology and Clinical Picture of Acute Rheumatic Fever.** LAZAR, H. P., MAAS, G. I., LIPSCOMB, W. R., HAMMOND, J. H., and RANTZ, L. A. (1957). *A.M.A. Arch. intern. Med.*, **100**, 604. 6 figs, 24 refs.

A great increase in enlistment of U.S. Air Force recruits occurred in January, 1955, because of the discontinuance of a law giving certain benefits to recruits, with effect from January 31 of that year. This resulted in an epidemic of rheumatic fever at Parks Air Force Base, California, where 58 cases were seen over the subsequent 6-month period, an incidence of 4.1 cases per 1,000 per year, compared with the previous experience of between 0.5 and 1.8 per 1,000 per year at this base and with 1.1 per 1,000 per year for the whole United States Air Force in 1951.

Bacteriological examination showed that one-half of those who had been at the base for 60 days carried Group-A  $\beta$ -haemolytic streptococci in their throat. All but one of those who developed rheumatic fever (as defined by the modified Duckett Jones criteria) were between 17 and 21 years of age, and eleven (19 per cent.) gave a history of a previous attack of rheumatic fever. Polyarthritides occurred in 47 (81 per cent.), monarthritides in nine (16 per cent.), fever in 56 (97 per cent.), and a new and significant heart murmur in eleven (19 per cent.). The P-R interval was prolonged [but no definition is

given] in fourteen cases (24 per cent.).  $\beta$ -Haemolytic streptococcal infection could be detected by culture or antibody response in 47 (81 per cent.) of the cases, while the antistreptolysin titre was raised (above 200 units) in 45 (78 per cent.).

Treatment consisted in a 10-day bactericidal course of penicillin by mouth, followed by prophylactic dosage. Salicylates were administered together with cortisone to patients with carditis and alone to those without carditis. The dosage of salicylates was 10 g. per day for an average of 75 days. Cortisone maintenance dosage never exceeded 100 mg. a day, and was continued for an average of 63 days. In 91 per cent. of the cases treatment was instituted within 2 weeks of the onset. Comparison of the course of the disease in the present series with that in previous epidemics in the pre-cortisone era led the authors to conclude that steroids have not apparently altered the course of rheumatic fever, and that the use of cortisone with salicylates does not seem to offer any distinct advantages over salicylates alone. Despite the apparent mildness of the epidemic fifteen (26 per cent.) of the patients developed valvular heart disease of a grade sufficient to result in discharge from the Service.

E. G. L. Bywaters.

**Streptococcal Disease and Rheumatic Fever in Air Force Recruits. II. Prophylaxis with Tandem Oral Penicillin.**

LAZAR, H. P., MAAS, G. I., HARRISON, W., HAMMOND, J. H., and RANTZ, L. A. (1957). *A.M.A. Arch. intern. Med.*, **100**, 614. 1 fig., 10 refs.

As a result of the epidemic described in the preceding paper an oral penicillin prophylaxis programme was planned at Parks Air Force Base. When in December, 1955, 32 per cent. of throat cultures yielded  $\beta$ -haemolytic streptococci and the rate of admission to hospital for "sore throat" rose to 3.7 per 1,000 per week, all recent recruits were given 250,000 units of oral penicillin twice daily for 10 days, and all new recruits also received this prophylactic treatment after 14 days of residence (a total of 25,305 recruits). Despite a marked rise in enlistment and in the incidence of non-streptococcal upper respiratory infection, no increase in streptococcal infection occurred. [However, no decrease in the rate of between 1 and 3 per 1,000 occurred over this period.] In the protected population only four cases of "undoubted" rheumatic fever occurred, one owing to failure to take the tablets, two before prophylaxis could be effective, and only one after adequate prophylactic treatment.

E. G. L. Bywaters.

**Follow-up Experiences with Rheumatic Fever Patients treated with Adrenal Steroids.** GULOTTA, G. A., WARREN, J. E., and LAMOTTA, E. P. (1957). *Bull. St. Francis Hosp. (Roslyn)*, **14**, 35. 18 refs.

Brief details are given of the findings at follow-up examination of 358 children treated for acute rheumatic fever at the St. Francis Hospital, New York, the period of observation being 4 to 7 years. Cortisone or corticotrophin (ACTH) was given to 72 patients for periods of 28 days [the number of courses is not stated]; treatment

in the remaining patients (the controls) consisted in rest in bed and supportive measures. At follow-up examination, new heart murmurs had developed in 62 (22 per cent.) of the control group and in five of the group receiving hormone treatment. It was also found that 48 (16 per cent.) of the controls and 29 of those given hormones had either lost murmurs which were previously regarded as significant or had remained without murmurs.

The authors consider that these results lend support to the view that the administration of cortisone or corticotrophin in the acute phase of rheumatic fever reduces the degree of cardiac damage. *J. Warwick Buckler.*

**Tonsillitis and Rheumatic Fever.** ROGERS, L. S. (1958). *A.M.A. Arch. Otolaryng.*, 67, 569. 1 fig., 26 refs.

The author reviews 87 cases of acute rheumatic fever admitted to the Los Angeles County General Hospital during a 2-year period, with particular reference to preceding respiratory infection, the results of bacteriological and serological investigations, and the presence or absence of the tonsils. In nearly half the cases there had been a previous upper respiratory infection; in 39 per cent. culture of a throat swab was positive for  $\beta$ -haemolytic streptococci, and in 96 per cent. the serum anti-streptolysin-O titre was increased. In 85 per cent. of cases the tonsils were present and in 15 per cent. they had been removed at the time of the first attack. Recurrence occurred in half the total number of cases and was more common in patients on whom tonsillectomy had been performed, among whom also the incidence of heart disease and the mortality were slightly higher than in the remainder.

The figures here presented thus provide no evidence that tonsillectomy has any beneficial effect on the incidence or course of rheumatic fever and it is held that the indications for tonsillectomy in cases of acute rheumatism are the same as in any other case, though emphasis is laid on the danger of performing the operation during the active stage of the disease and on the value of the treatment of tonsillitis in children with penicillin and sulphadiazine as a precaution against the development of rheumatic fever. *F. W. Watkyn-Thomas.*

**Prophylaxis of Rheumatic Fever and Its Recurrences.** (La profilassi della malattia reumatica e delle sue recidive.) CESARI, M. (1958). *Med. soc. (Torino)*, 8, 106.

**Blood Antistreptolysin-O Level in Children with Rheumatic Fever.** (O poziomie antystreptolizyny o we krwi u dzieci z chorobą reumatyczną.) LEWENFISZ-WOJNAROWSKA, T., SUFICYŃSKA, M., KWAPIŃSKI, J., RAU, B., and BACZYŃSKA, K. (1958). *Pediat. pol.*, 33, 63. 5 refs.

**Significance of the C-reactive Protein Estimation in Streptococcal and Allied Disease.** DAWSON, S. F. (1957). *Arch. Dis. Childh.*, 32, 454. 4 figs, 12 refs.

### Chronic Articular Rheumatism (Rheumatoid Arthritis)

**Psychosocial Factors in the Epidemiology of Rheumatoid Arthritis.** KING, S. H., and COBB, S. (1958). *J. chron. Dis.*, 7, 466. 2 figs, 9 refs.

During 1951 and 1952 a health survey was carried out in Pittsburgh, Pennsylvania, and fuller interviews were obtained with 1,166 persons, who, among other things, were asked about arthritic symptoms. Three of these questions when taken together were regarded as a useful "index of rheumatoid arthritis", and the replies were considered to give a "positive" result in 200 cases. These individuals were then compared with the other 966 who had a "negative index", in respect of a number of social factors.

It was shown that a low income, a low educational standard, and termination of marriage were associated with a higher prevalence of a positive index in men. In the case of women, the most significant factors were a low educational standard, having borne four or more children, a lack of leisure time in the third decade of life, and worrying more than other people. Further analysis showed wide differences (up to 36-fold) in the prevalence rate of a "positive index" as between subjects falling into none of these categories and those falling into two or more. Among those interviewed, 478 subsequently underwent a complete physical examination, and although the number diagnosed as having rheumatoid arthritis was small, analysis of these patients with regard to the same social data showed similar trends. The authors consider that they have demonstrated certain associations between a positive "index of rheumatoid arthritis" and some social factors, and they suggest that these factors may be of aetiological importance.

*K. C. Robinson.*

### Role of the Nervous System in Rheumatoid Arthritis.

(Le rôle du système nerveux dans la polyarthrite chronique évolutive.) MICHOTTE, L. J. (1958). *Rev. Rhum.*, 25, 93. 13 refs.

The author draws attention to the fact that apart from the arthropathies associated with tabes and syringomyelia such lesions also occur in other diseases of the nervous system, citing as examples the arthritis occasionally observed on the affected side in hemiplegia and the deformity and bone destruction seen in paralysis agitans. The latter lesion may be unilateral when the disease is more advanced on one side. This irregular asymmetric distribution appeared to the author to suggest the influence of the autonomic rather than the central nervous system, and he has attempted, therefore, to explore the functional pathology of the autonomic nervous system in rheumatoid arthritis.

In man an intravenous injection of adrenaline causes contraction of the spleen, which may be visualized radiologically after an intravenous injection of ethyl iodostearate which collects in the spleen. In controlled experiments the author was able to show that noradrenaline does not cause contraction of the spleen in patients with rheumatoid arthritis. The ratio of excretion of noradrenaline to adrenaline in the urine of

normal subjects ranges from 5 : 1 to 3·4 : 1, but among rheumatoid patients he found this ratio to be 1 : 3·6. After an injection of noradrenaline the excretion of this hormone in rheumatoid arthritic patients was increased four to six times, proving that the imbalance is not due to renal insufficiency. When hydrocortisone was given to five rheumatoid arthritic patients, the ratio of the urinary excretion of noradrenaline to adrenaline changed from 1 : 4 to 14 : 1. The enzyme which is believed to be responsible for the destruction of noradrenaline in healthy subjects is mono-amino-oxidase. Its action is inhibited by cortisone and also by procaine. Transfusion of five patients over 8 hours with one litre of 0·1 per cent. solution of procaine changed the ratio of noradrenaline to adrenaline excreted from 0·5 : 1 to 4 : 1. Iproniazid has been shown independently to be very effective in producing temporary amelioration of the symptoms of rheumatoid arthritis, although isoniazid has no such effect. Since it is known that iproniazid is an inhibitor of the enzyme mono-amino-oxidase while isoniazid is not, it would therefore appear that excessive destruction of noradrenaline owing to some fault in the autonomic nervous system plays a part in the mechanism of rheumatoid arthritis.

William Hughes.

#### Suppurative Arthritis complicating Rheumatoid Arthritis.

KELGREN, J. H., BALL, J., FAIRBROTHER, R. W., and BARNES, K. L. (1958). *Brit. med. J.*, **1**, 1193. 5 refs.

The authors describe twelve cases of suppurative arthritis complicating rheumatoid arthritis observed at the Rheumatism Research Centre, Manchester, during the years 1950-57. There were seven males and five females, and their ages ranged from 37 to 63 years. The infecting organism was *Staphylococcus aureus* in ten cases and coliform bacilli in two cases. Blood culture was positive at some time in seven cases; in six of these a strain of *Staph. aureus* was isolated and in one a coliform organism. There were seven deaths in the series and five patients recovered. Multiple infection of joints occurred in every case, and in most cases abscesses had formed in other tissues. Frequently rheumatic nodules suppurated and discharged; osteomyelitis of the ribs occurred in two cases and osteomyelitis of a vertebra in one. The rheumatoid arthritis was rated as severe in nine cases when first observed. Cortisone or corticotrophin had been given in four cases.

The symptoms were those which might be expected locally in a severe arthritis, and these were apt to be mistaken for an exacerbation of the rheumatoid disease. All patients had high fever, often with suggestive swinging temperatures. Most cases had a leucocyte count of 10,000 per c.mm. or more with an excess of polymorphonuclear cells, but in three cases the count did not exceed 6,000 per c.mm. The serum protein level was low in eleven cases, the albumin content being most affected. The staphylococcus isolated was frequently penicillin-resistant, but sensitive to other antibiotics in current use. The authors consider that if the possibility of suppurative arthritis is borne in mind the diagnosis could be established earlier and the appropriate antibiotic therapy instituted.

William Hughes.

#### Peripheral Neuritis associated with Rheumatoid Arthritis.

IRBY, R., ADAMS, R. A., and TOONE, E. C. (1958). *Arthrit. and Rheum.*, **1**, 44. 4 figs, 12 refs.

In six cases of rheumatoid arthritis in which the disease had been present for 13 to 20 years, signs of peripheral neuritis were detected. These patients, all of whom were seen during the course of 2 years and five of whom were male, complained predominantly of numbness, tingling, and burning of the extremities. Sensory changes were more marked than motor, and in all cases the knee-jerks were retained. The condition is considered to be due to an inflammatory lesion of the blood vessels supplying the nerves affected. All the patients had been receiving steroid therapy for some time, and there is some indication that this may be a factor in the aetiology.

G. S. Crockett.

#### Arteriolar Involvement in Rheumatoid Arthritis. (La sofferenza arteriolare nel reumatismo cronico primario.)

SERNERI, G. G. N., and SCIAGRÀ, A. (1957). *Riv. crit. Clin. med.*, **57**, 211. 5 figs, bibl.

In studies reported from the University of Florence, finger plethysmography was carried out in fourteen patients with chronic rheumatoid arthritis, observations being made first at ordinary room temperature (18° C.), then after immersion of the hand for 5 min. in water at 45° C., and lastly after 5 min. immersion in water at 3 to 5° C. In two cases the tracings were normal and in four others there were very slight abnormalities. In the remaining eight cases, which are reported in detail, the abnormal responses are described as of the "Raynaud type" or of the "noradrenaline type". The implications of these findings are discussed.

David Friedberg.

#### Rehabilitation of the Rheumatoid Cripple: a Five-Year Study.

LOWMAN, E. W. (1958). *Arthrit. and Rheum.*, **1**, 38.

The response of patients disabled by rheumatoid arthritis to an intensive programme of physical rehabilitation was studied by means of a 4-page list of activities concerned with the patient's everyday needs. By entering the date on which the patient becomes able to perform each activity independently, his physical capabilities at any moment can be accurately assessed and his progress recorded. It was found that, of seventeen severely disabled patients whose average age was 46 and in whom the disease had been present for an average of 8 years, six were rendered completely self-sufficient and five of these retained their self-sufficiency throughout 3 years of follow-up. Of 21 less severely disabled, whose average age was 40 and in whom the average duration of the disease was 8 years, seventeen became totally self-sufficient and twelve of these remained so. Medical treatment was continued during the rehabilitation programme.

Of all the factors contributing to a successful result, the desire and willingness of the patient to take part in his or her own restoration was judged to be the most important. [This must be the experience of all who are engaged in this kind of work.]

G. S. Crockett.



**Bentonite Flocculation Test for Rheumatoid Arthritis.**

BOZICEVICH, J., BUNIM, J. J., FREUND, J., and WARD, S. B. (1958). *Proc. Soc. exp. Biol. (N.Y.)*, **97**, 180. 4 refs.

Particles of bentonite (a North American clay) were used by Bozicevich and others (*Publ. Hlth Rep. (Wash.)*, 1951, **66**, 806) to adsorb antigenic material from *Trichina* for use in a serological test for trichiniasis. In the present paper the authors describe the use of a slight modification of this method in the detection of the serum factor characteristic of rheumatoid arthritis, bentonite particles coated with human  $\gamma$  globulin (Fraction II of Cohn) flocculating when mixed with serum containing the rheumatoid factor, but not when mixed with control sera.

The stock suspension of bentonite in water is prepared by a method entailing two centrifugations [the details of which are important and should be consulted in the original]. Lyophilized Fraction II prepared from normal human serum is dissolved in veronal buffer and absorbed on to the bentonite particles, using four centrifugations with washing. The serum to be tested is first heated to 56° C. for 30 min. and serial 2-fold dilutions made in saline. To 1 ml. of each dilution on a ringed slide is added one drop (about 0.025 ml.) of the suspension of sensitized particles by means of a capillary pipette, the slide is rotated mechanically 100 to 120 times per minute for 20 min., and is then examined for flocculation under low-power magnification, the degree of flocculation being graded from 0 to 4+. The reaction is regarded as positive when 2+ or stronger clumping occurs in a serum dilution of 1 : 32 or higher.

Of 41 sera from adults with "unquestionable" rheumatoid arthritis, 32 (78 per cent.) gave a positive bentonite-fixation reaction. There was some association of a positive reaction with the presence of subcutaneous nodules, but this was not very close. Of the nine sera which gave a negative reaction, six also gave negative results in agglutination tests with sheep erythrocytes sensitized with euglobulin. Of 163 sera from normal subjects and patients with diseases other than rheumatoid arthritis, three gave positive reactions; one of these patients had systemic lupus erythematosus, one macro-globulinaemia, and one acute leukaemia. A direct comparison between the results of the bentonite test and the sensitized sheep cell test was carried out on 64 sera from cases of rheumatoid arthritis, with concordance in 98 per cent.

E. G. L. Bywaters.

**Further Observations on the Use of 4-Aminoquinoline Compounds in Patients with Rheumatoid Arthritis or Related Diseases.** SCHERBEL, A. L., HARRISON, J. W., and ATDJIAN, M. (1958). *Cleveland Clin. Quart.*, **25**, 95. 2 figs, 27 refs.

The authors report from the Cleveland Clinic, Ohio, the results of treatment of 805 patients suffering from rheumatoid arthritis or related diseases with 4-aminoquinoline compounds. Chloroquine phosphate was given in doses of 125 to 250 mg. daily, and hydroxychloroquine sulphate in doses of 600 mg. daily; of the 106 patients treated with 4-aminoquinoline compounds

alone, 46 received chloroquine and the other sixty received hydroxychloroquine.

Improvement did not begin to appear until 6 to 12 weeks had elapsed and it then continued slowly for 6 to 12 months. After one year 24 patients were in complete remission, 41 showed major improvement, 33 minor improvement, and eight no improvement. Clinical improvement was not hastened by larger initial dosage, but with this aim in view 194 patients were given prednisone or prednisolone in doses of 3 to 7.5 mg. daily and also iproniazid, in addition to a 4-aminoquinoline compound. Major improvement occurred in 83 per cent. of the patients in this group. Side-effects were noted in 440 of the 805 patients treated. These were transient and disappeared spontaneously in 67 per cent., but necessitated reduction of dosage or temporary cessation of treatment in 26 per cent. and precluded further use of the drugs in 7 per cent. The manifestations were dermatological in 12 per cent., gastro-intestinal in 17 per cent., and nervous or vascular in 49 per cent., this last group including difficulty in visual accommodation, headaches, vestibular dysfunction, tinnitus, nervousness, insomnia, and mental confusion. The desirable and undesirable features of this form of treatment are discussed, and the orderly withdrawal of the supplemental agents as improvement occurs is stressed. In general, these drugs "effectively maintained suppression of the disease in 83 per cent. of 194 patients followed for 18 months".

C. E. Quin.

**Treatment of Rheumatoid Arthritis with Quinacrine and Chloroquine.** [In English.] ENGESET, A. (1958). *Acta rheum. scand.*, **4**, 28. 2 figs, 16 refs.

The author gives an account of his use of quinacrine and chloroquine in the treatment of rheumatoid arthritis at Rogaland Hospital, Stavanger, Norway, since 1952. Apart from toxic effects no differences in the actions of the two drugs were observed, and they are discussed together. The usual doses were: quinacrine, 100 mg. daily for a year, and chloroquine, 250 mg. daily for a year; there were long follow-up periods, up to 4 years in some instances.

At first only patients with severe, active disease were treated, and the 41 cases now reported represent less than one-third of the total number admitted with rheumatoid arthritis. Of these, 34 experienced subjective and objective remission. The erythrocyte sedimentation rate fell in 24 of the 31 cases in which it was high initially. In the majority of cases relapse occurred about 3 months after treatment was stopped. A second course of treatment produced the same response as the first course, but this was only possible in about half the patients who relapsed, the appearance of toxic effects in fourteen cases necessitating discontinuance of treatment before the end of the first year. The complications included vomiting, psychosis, and dermatitis, and occurred chiefly in those given quinacrine; chloroquine did not give rise to any serious toxic reactions.

The author admits that evaluation of the results is difficult as placebo effects and spontaneous improvement



have both to be considered; but he is impressed by the uniformity in time at which improvement began after starting treatment and subsequent relapse occurred when treatment was stopped, and by the conformity between subjective and objective changes. *K. C. Robinson.*

#### Hydrocortisone and Prednisolone in Rheumatoid Arthritis.

ROBINSON, R. G. (1958). *Med. J. Aust.*, 1, 523. 14 refs.

In a careful study carried out at the Royal North Shore Hospital, Sydney, the effects of hydrocortisone and its newer derivative prednisolone were compared in 28 cases of rheumatoid arthritis. After a base-line of activity had been established by preliminary examination, treatment was started with hydrocortisone in a dose which achieved reasonable and measurable suppression of the arthritis. After a varying interval comparative tests of function were carried out, prednisolone was substituted for the hydrocortisone, tablet for tablet, without the knowledge of patient or attendants, and further comparative observations were made.

Improvement in the general condition occurred with hydrocortisone and in almost all cases there was additional improvement on changing to prednisolone. As judged by Steinbrocker's system of grading, improvement in the joints followed the same pattern. The haemoglobin content of the blood increased during treatment with prednisolone, but not with hydrocortisone. The water and salt balance was not disturbed by prednisolone in moderate dosage.

The most marked difference between the two drugs was in the incidence of obesity, oedema, and facial rounding, which was lower with prednisolone. However, there was a slightly greater frequency of dyspepsia with the newer steroid. *Oswald Savage.*

#### Heart Lesions in Rheumatoid Disease. CRUICKSHANK, B. (1958). *J. Path. Bact.*, 76, 223. 12 figs, bibl.

In a small initial series of patients with rheumatoid arthritis (*Quart. J. Med.*, 1956, 25, 313; *Abstr. Wld Med.*, 1957, 21, 125) a higher incidence of cardiac lesions was found than had previously been reported, and it was therefore decided to investigate a larger series. The hearts from one hundred necropsies on patients with rheumatoid conditions were studied. Of these, 33 were males and 67 females aged between 2½ and 85 years; the duration of illness was 3 months to 33 years. No known cases of ankylosing spondylitis were included. Six blocks were cut from standard sites in the heart in 65 cases, and a smaller number of blocks in another thirty; in five no microscopical study was possible. The lesions were compared with those in 267 cases of rheumatic heart disease without arthritis.

In five cases rheumatoid granulomata were found with the characteristic fibrinoid necrosis and palisade usually seen in the rheumatoid subcutaneous nodule. These were situated at the mitral ring and valve, in some chordae, and also at the aortic and tricuspid rings. There were other visceral manifestations in all five cases, and the arthritis was active in two of them. Active

rheumatic carditis with Aschoff nodules was seen in one case, while a few others showed old valvular lesions of the rheumatic type. There was evidence of active or healed endocarditis without definite rheumatic or rheumatoid features in nine hearts. The appearances were those of chronic inflammation with fibrosis and calcification around the valves. Active myocarditis, evidenced by small focal interstitial collections of chronic inflammatory cells, frequently near the mitral ring, was present in eleven cases. In twenty cases there was active or healed arteritis, and fifteen examples of old and one of active pericarditis were seen. One heart showed amyloidosis.

The over-all incidence of 33 cases with cardiac lesions out of a total of one hundred rheumatoid cases is similar to that found in other surveys, but the author has attributed a greater number of the lesions to the rheumatoid process itself. The heart lesions appeared to occur in the more severe cases of rheumatoid arthritis.

[The inclusion of laboratory data, especially results of the differential agglutination test, would have been helpful but there is much valuable information which should be studied in full.] *G. Loewi.*

#### Contribution to the Study of Juvenile Rheumatoid Arthritis and its Cervical Localization. (Contribution à l'étude de la polyarthrite chronique évolutive de l'enfant, ses localisations cervicales.) LE BAUDOUR, J., and FREYBERG, R. H. (1958). *Sem. Hôp. Paris*, 34, 1120. 7 figs, 14 refs.

The authors have reviewed the records of 28 cases of juvenile rheumatoid arthritis, 22 in females, seen during the past 15 to 20 years at the New York Hospital-Cornell Medical Center, New York; all but five of the cases had been under observation for more than 4 years. In thirteen there was clinical and radiological evidence of affection of the cervical spine, and in three others clinical signs only, while there were two cases of ankylosing spondylitis in children.

The cervical spine is most frequently affected at the level of C2 or C3, the first sign being irregularity of the articular surfaces of the posterior joints. This is followed by fusion of the facets, and then in many cases by narrowing of the corresponding disk space. Some atrophy of the vertebral bodies concerned may occur, but complete fusion of the vertebral bodies was not seen in this series. Subluxation of the first cervical vertebra to the second was discovered in two cases. Since this caused restriction of cervical movement the authors urge that such cases should be examined and treated with circumspection. Underdevelopment of the mandible was noted in eight cases, and the authors suggest that the abnormal stiffness and posture of the head and neck, together with inflammatory changes in the temporo-mandibular joints, may be responsible for this development. In none of these cases did radiography reveal any changes in the dorsal or lumbar spine; some minor sacro-iliac abnormalities were found in three patients grown to adult life, but these changes appeared to be different from those seen in the cases of ankylosing spondylitis.

*B. E. W. Mace.*

**Eye Changes of Still's Disease.** SMILEY, W. K. (1958). *Proc. roy. Soc. Med.*, **51**, 597. 6 figs, 1 ref.

Two cases and the encouraging results of treatment are described. Both showed the typical ocular triad of Still's disease—iridocyclitis, band-shaped corneal opacities dispersed by chelation with sodium versenate, and complicated cataracts. Of the 200 children with Still's disease seen in the unit, twelve had iridocyclitis, and, of these, half had band-shaped opacities, and a quarter complicated cataracts. The occurrence of ocular changes was not related to the severity of the disease.

M. Starbuck.

**Preliminary Experience in the Prophylaxis of Rheumatoid Arthritis.** (Esperienze preliminari sulla profilassi della malattia reumatoide.) SCHIAVETTI, L., and GOSPODINOFF, A. (1957). *Policlinico, Sez. prat.*, **64**, 1529. 2 figs.

**Studies in Anaemia during the Course of Rheumatoid Arthritis.** [In English.] EKLUND, C. (1958). *Acta rheum. scand.*, **4**, 135. 11 refs.

**Physical Aetiological Factors influencing the Appearance and Course of Rheumatoid Arthritis.** (Les conditions physiques étiologiques influençant l'apparition et l'évolution de la P.C.E.) MICHEZ, J. (1958). *J. belge Med. phys. Rhum.*, **13**, 87.

**Skin Complications of Gold Treatment.** [In English.] BOGG, A. (1958). *Acta rheum. scand.*, **4**, 86. 2 figs.

**Chloroquine in Rheumatoid Arthritis.** (Klorokvin vid reumatoid artrit.) KALLIOMÄKI, J. L. (1958). *Nord. Med.*, **59**, 726. 11 refs.

**Extracellular Fluid Phase in Rheumatoid Arthritis.** [In English.] KALLIOMÄKI, J. L., KIRPILÄ, J., KOSKINEN, H.-M., and LAINE, V. A. I. (1958). *Acta rheum. scand.*, **4**, 79. 1 fig., 37 refs.

**Long-term Treatment of Chronic Articular Rheumatism with a Combination of Phenylbutazone and Prednisone.** (Dauerbehandlung des chronischen Gelenkrheumatismus mit einer Butazolidin-Prednison-Kombination.) BARCZYK, W., and RÖTH, G. (1958). *Med. Klin.*, **53**, 1175. 15 refs.

**Treatment of Rheumatoid Arthritis with Benemid (Preliminary Communication).** (Tratamiento de la artritis reumatoidea con benemid.) RUIZ MORENO, A., and HALPERIN PINES, A. M. (1958). *Arch. argent. Reum.*, **21**, 51. 2 refs.

**Effect of Marsilid (Iproniazid) in Patients having Rheumatoid Arthritis and the Theoretical Causal Role of Certain Amine Oxidases.** (Les effets du Marsilid (Iproniazid) chez des patients atteints d'arthrite rhumatoïdale et le rôle causal théorique de certaines amineoxydases.) SCHERBEL, A. L. (1958). *J. belge Med. phys. Rhum.*, **13**, 135. 4 refs.

**Planning of Therapeutic Trials in Rheumatoid Arthritis.** (Terapeutisk eksperiment: diskussion af forsøgstiltingen ved reumatoid arthritis.) ERLÉNDSOHN, F. (1958). *Ugeskr. Laeg.*, **120**, 809. 12 refs.

**Investigations into the Clinical Significance of the Waaler-Rose Haemagglutination Reaction.** (Untersuchungen zur klinischen Bedeutung der Hämagglutinationsreaktion nach Waaler und Rose.) SCHEIFFARTH, F., FRENGER, W., and GRIMM, H. (1958). *Ärzt. Wschr.*, **13**, 575. 25 refs.

**Significance of the L.E. Phenomenon in Rheumatoid Arthritis.** (La signification du phénomène L.E. dans la polyarthrite chronique évolutive.) GOSLINGS, J., and HUIJMAN, W. (1958). *J. belge Med. phys. Rhum.*, **13**, 113. 2 figs, 20 refs.

**Thyroidectomy and Rheumatoid Arthritis.** [In English.] KALLIOLA, H., KALLIOMÄKI, J. L., and RINTALA, A. (1957). *Ann. Med. intern. Fenn.*, **46**, 97. 6 refs.

#### (Osteo-Arthritis)

**Osteo-Arthritis of the Knee: Treatment by Local Injection of Salicylate Compounds.** ROSS, K. A., MAYER, J. H., and SHEPHERD, M. M. (1958). *Brit. med. J.*, **1**, 1040. 23 refs.

The authors report from Pembury Hospital, Pembury, Kent, the results of treating 53 patients (12 male and 41 female) aged 34 to 79 suffering from osteo-arthritis of the knees with intra-articular injections of 5 per cent. benzyl salicylate in arachis oil in a dose of 0.1 to 0.3 ml. injected by means of a tuberculin syringe, usually without anaesthetic, such injections being given at weekly intervals for 6 to 8 weeks. In addition, eighteen knees were also treated by intraosseous injections of 0.2 per cent. aqueous solution of salicylic acid with 1 per cent. sodium citrate under a general anaesthetic. The indication for giving an injection into the bone was persistent pain as the main symptom after completion of the course of intra-articular injections. Intraosseous injections were given above the joint into the medial condyle of the femur distal to the adductor tubercle, and below it into the medial condyle of the tibia two fingers' breadth below the joint line, a dose of 50 to 80 ml. of the solution being divided equally between the two sites.

An analysis of the patient's condition was made before the start of treatment and at a mean of 6 months after its completion, and compared with the progress in the 6 months before treatment, the assessment (made by an assessor not concerned in the trial) being based on the amount of pain, the range of movement of the knee, and

the effect on function as shown by greater ease in performing various everyday activities. The patient was also asked to make his own assessment. The results of treatment of 88 knees were considered to be "excellent" in 24, "good" in 27, "fair" in 16, and "poor" in 21; thus 67 knees showed improvement (in 51 considerable) in the 6 months after starting treatment, whereas only six had done so in the 6 months before this treatment. The patients themselves were "enthusiastically pleased" with the results in 35 knees, "pleased" in 29, "doubtful" in fifteen, and considered the treatment "not worth while" in nine. The results in patients receiving intra-osseous injections in addition were very similar to those for the whole series. [There was no control group.]

C. E. Quin.

**Extended Sympathectomy in the Treatment of Chronic Arthritis.** HERTFORD R. A. (1957). *J. Amer. Geriat. Soc.*, 5, 904. 7 figs, 22 refs.

The author of this paper from St. Agnes Hospital, White Plains, and Grasslands Hospital, Valhalla, New York, describes a technique of "extended lumbar sympathectomy", designed to denervate and render painless diseased joints of the lower limbs, which he has used in the treatment of seven patients with chronic arthritis involving those limbs and intractable pain in the knees and hips. The operation consists in removal of lumbar sympathetic ganglia 2, 3, and 4, with accessory ganglia and decussating fibres (by vertebral body scarification), the retroperitoneal route being employed. The operation was successful in relieving articular pain in six of the seven patients. No neuropathic joints were observed.

G. S. Crockett.

**Conservative Management of the Osteo-Arthritic Knee.** KEELER, K. C. (1957). *J. Amer. Geriat. Soc.*, 5, 1009.

This is a survey of 39 cases of osteo-arthritis of the knee treated conservatively in patients whose ages ranged from 51 to 82 years. Seven of these patients were bedridden. Symptoms varied from pain on arising from a chair or ascending stairs to pain on ordinary walking. Pain at night was present in 25 per cent. of patients.

It is suggested that mechanical disorders rather than intra-articular changes are the major source of symptoms. One-third of the affected knees showed genu varum, and three-quarters showed lateral instability. Nearly all patients were obese. Initial treatment consisted of rest and the application of heat, and later non-weight-bearing exercises were started. The correction of skeletal misalignment was attempted by the use of wedging casts or passive stretching for flexion contractures, and by a long leg-brace to control instability. If the knee remained painful during weight-bearing, the use of two crutches occasionally gave partial rest to the affected joints.

P. Ring.

**Surgery of the Osteo-Arthritic Hip.** WILES, P. (1958). *Brit. J. Surg.*, 45, 488.

This is a general review of the indications for and the results of surgery in the osteo-arthritic hip. There is an account of the evolution of hip arthroplasty, including

the author's own work on the construction of a stainless steel acetabulum and femoral head, and a general consideration of the problems of prosthetic replacement in the hip.

Arthrodesis of the hip is regarded as the operation of choice in patients under the age of 40, simple excision of the joint surfaces followed by fixation with a Triffin nail being performed. In older patients, whilst arthrodesis is often preferred, McMurray's intertrochanteric osteotomy has proved satisfactory provided there is a good range of flexion in the joint. When the hip is stiff and undergoing progressive degenerative changes, cup arthroplasty is recommended because of the increase in the range of joint movement which may be obtained. In the elderly, replacement arthroplasty has the advantage of giving a more rapid result. The author is reluctant to fuse the hip in the presence of degenerative changes in the spine.

There are two interesting graphs showing the breakdown of types of operation, one according to age and the other according to the year in which the operation was done. Cup arthroplasty, which figured in all lists of operations in the last decade, has fluctuated in popularity as the use of prostheses has been alternately introduced and abandoned.

P. Ring.

**Degenerative Joint Disease in Castrated Mice. I. Effects of Ovariectomy at Various Ages.** SILBERBERG, R., GOTO, G., and SILBERBERG, M. (1958). *A.M.A. Arch. Path.*, 65, 438. 9 refs.

In female mice (strain C57BL), ovariectomy performed at 1, 6, or 12 months retarded articular ageing and decreased the incidence and severity of osteo-arthritis as compared with control mice. The protective effect was most noticeable when castration took place at 6 months. Since ovariectomy did not lead to an increased incidence of osteo-arthritis, endogenous oestrogen does not protect the female mouse against this condition. The well-known lower susceptibility of the female to osteo-arthritis as compared with that of the male can not therefore be accounted for by ovarian activity.

G. W. Csonka.

**II. Effects of Orchidectomy at Various Ages.** SILBERBERG, R., THOMASSON, R., and SILBERBERG, M. (1958). *A.M.A. Arch. Path.*, 65, 442. 10 refs.

The articular effects of orchidectomy in male mice (strain C57BL and DBA) were investigated. When castration was carried out at one month of age, articular ageing and evolution of osteo-arthritis was significantly delayed as compared with control mice. Castration performed at 6 or 12 months of age did not affect the incidence of osteo-arthritis, but the joint lesions were less severe than in non-castrates. A comparison of the articular effects of orchidectomy and ovariectomy shows that the sex differences in osteo-arthritis present in non-castrated mice is to a large extent eliminated in the castrates. These observations suggest that the sex hormones play an important part in the susceptibility to the disease of male and female mice respectively.

G. W. Csonka.



**Natural History of Degenerative Joint Disease in Small Laboratory Animals. 5. Osteo-Arthritis in Guinea-Pigs.** SILVERSTEIN, E., and SOKOLOFF, L. (1958). *Arthrit. and Rheum.*, **1**, 82. 1 fig., 12 refs.

Naturally occurring degenerative joint disease is described for the first time in guinea-pigs at the National Institute of Arthritis and Metabolic Diseases, Bethesda, Md. Twenty animals of two strains were studied. Thirteen animals were killed and seven died at 29 to 51 months of age. In the sixteen animals which survived to 30 months of age and more, degenerative joint disease was found to be present. Osteophyte formation was observed with and without erosion of the articular cortex. The predominant distribution in the knees suggests that weight-bearing was not the sole cause of the degenerative changes.

G. W. Csonka.

**Clinical Features and Pathogenesis of Heberden's Nodes.** (Beitrag zur Klinik und Pathogenese der Heberden-schen Knoten.) LEMKE, G. (1958). *Derm. Wschr.*, **137**, 518. 2 figs, 10 refs.

**Pre-Tibial Subcutaneous Calcification in Osteo-Arthritis.** (Calcifications pré-tibiales sous-cutanées dans le rhumatisme chronique dégénératif.) FRANÇON, F., BELOT, R., and PERRIER-GERBAY, Y. (1958). *Lyon méd.*, **199**, 735. 1 fig.

**Current Views on the Management of Osteo-Arthritis of the Hip.** WILLIAMS, P. F. (1958). *Med. J. Austr.*, **2**, 293.

**Are Repeated Intra-Articular Injections of Hydrocortisone Necessary in Osteo-Arthritis of the Hip?** (Faut-il continuer à faire aux coxarthroses des injections intra-articulaires d'hydrocortisone?) LAURENT, F. (1958). *Rhumatologie*, **10**, 76.

**Natural History of Osteo-Arthritis of the Hip.** (Histoire naturelle de la coxarthrose.) COSTE, F., and LAURENT, F. (1958). *Sem. Hôp. Paris*, **34**, 1551. 16 figs.

**Medical Treatment of Osteo-Arthritis of the Hip.** (Le traitement médical de la coxarthrose.) COSTE, F., and LAURENT, F. (1958). *Sem. Hôp. Paris*, **34**, 1561. 2 figs.

**Results of Non-Operative Treatment of Osteo-Arthritis of the Hip.** (Résultats actuels du traitement non sanglant de la coxarthrose.) COSTE, F., and LAURENT, F. (1958). *Sem. Hôp. Paris*, **34**, 1566.

**Acetabular Protrusion. A Study of 92 Cases.** (Les protrusions acétabulaires. A propos de 92 cas personnels.) COSTE, F., LAURENT, F., and PÉROL, R. (1958). *Sem. Hôp. Paris*, **34**, 1568. 5 figs, 17 refs.

**Indications for Surgery in Osteo-Arthritis of the Hip.** (Indications chirurgicales dans les coxarthroses). JUDET, R., and JUDET, J. (1958). *Rev. Rhum.*, **25**, 274.

### (Spondylitis)

**Prostatitis and Ankylosing Spondylitis.** MASON, R. M., MURRAY, R. S., OATES, J. K., and YOUNG, A. C. (1958). *Brit. med. J.*, **1**, 748. 2 figs, 42 refs.

An association between prostatitis and ankylosing spondylitis is not a new finding, but it is still not clear whether the two conditions are causally related. In this paper from the London Hospital, a study is reported of the incidence of prostatitis in 54 male patients with ankylosing spondylitis, 59 with Reiter's disease, and 86 with rheumatoid arthritis.

Reiter's disease was diagnosed on the presence of non-gonococcal urethritis associated with arthritis of acute onset and a variable, often relapsing, course. Conjunctivitis occurred in 24 of the 59 cases, uveitis in six, and keratoderma blennorrhagica in six. From each patient five samples of fluid were obtained by prostatic massage and examined microscopically in a high-power dark field. The criterion for diagnosis of chronic prostatitis was a minimum of ten pus cells per high-power field. By this method chronic prostatitis was demonstrated in 45 (83 per cent.) of the patients with ankylosing spondylitis, 28 (33 per cent.) of those with rheumatoid arthritis, and 56 (95 per cent.) of those with Reiter's disease.

The authors do not consider that the difference between the group with ankylosing spondylitis and with rheumatoid arthritis in respect of the incidence of prostatitis is due to the different mean age of the patients; there is no evidence that chronic prostatitis is commoner in younger than in older males. The incidence of chronic prostatitis in healthy males is reported to be 20 to 25 per cent.; the incidence in rheumatoid arthritis in this series thus appears to be close to that found in the general population of the same age group.

Radiological examination of the sacro-iliac joints of all the patients revealed unequivocal bilateral sacro-iliitis in 49 of the cases of ankylosing spondylitis, seven cases of rheumatoid arthritis, and nineteen of Reiter's disease—findings which might be taken to indicate that there is a causal association between chronic prostatitis and sacro-iliitis. However, the authors do not find much support for this in their figures; in all eleven cases of ankylosing spondylitis with a normal prostatic fluid there was unequivocal bilateral sacro-iliitis.

The high incidence of chronic prostatitis in ankylosing spondylitis remains unexplained. Kenneth Stone.

**The True Clinical Picture of Ankylosing Spondylitis (Rheumatic Pelvo-Spondylitis).** (Le vrai visage de la spondylarthrite ankylosante (pelvi-spondylite rhumatismale). SÈZE, S. DE (1958). *Bull. Acad. nat. Méd. (Paris)*, **142**, 412.



## (Miscellaneous)

**Study of Abnormal Mobility of the Knee-Joint and more particularly of the "Drawer Sign" in Rheumatic Conditions.** (Étude des mobilités anormales du genou et plus particulièrement du signe du tiroir antérieur dans les affections rhumatismales.) LEROY, J. (1957). *Rev. Rhum.*, 24, 806. 4 figs, 19 refs.

Fixation of the knees in a bad position is commonly met with in advanced rheumatoid arthritis and contributes to a large extent to chronic invalidism, but before this stage is reached there is often in these patients abnormal mobility of the knee-joints, accompanied by the appearance of the "drawer sign". This term was coined in 1919 by Rocher to describe a phenomenon which he attributed to injury to the cruciate ligament, but abnormal mobility of the knee-joint had been noted since 1875. The sign is elicited as follows: with the patient's muscles thoroughly relaxed the knee is flexed to a right angle and the upper part of the tibia firmly grasped and pulled forwards; if the sign is positive the tibia is clearly felt to slide forward (like a drawer) and when released returns immediately to its former position. In some cases the amount of displacement may be considerable.

Altogether 168 adult knees were examined. In forty normal knees the sign was absent. In 48 patients with non-rheumatoid involvement of the knee the sign was positive 8 times (one case of gout, three of ankylosing spondylitis, one of osteochondritis, two post-poliomyelitic cases, and one of Sudeck's atrophy). In forty osteoarthritic knees, of the type called by Françon and Weissenbach "dry lipo-arthritis", the sign was detected only once. Of forty cases of rheumatoid arthritis, the sign was present in 29 (72.5 per cent.), being bilateral in 21 and unilateral in eight; the ages of these patients ranged from 20 to 70 years. The sign may become positive within a few months of the onset of the disease, tends to persist for a long time, and disappears when the range of movement is grossly restricted or ankylosis sets in. Although the sign is not specific, it helps in differentiating rheumatoid arthritis from osteo-arthritis. Its mechanism appears to depend on a combination of excessive wear of the joint, stretching of the ligaments, and wasting of the quadriceps muscle.

D. Preiskel.

**Radiological Changes in Reiter's Syndrome and Arthritis associated with Urethritis.** MURRAY, R. S., OATES, J. K., and YOUNG, A. C. (1958). *J. Fac. Radiol. (Lond.)*, 9, 37. 13 figs, 16 refs.

In this article from the London Hospital the authors report a study of 53 patients suffering from Reiter's syndrome. All had arthritis associated with urethritis, but the conjunctivitis which constitutes the third feature of the syndrome tended to be mild and short-lived, and in 34 cases was absent. Elimination of concurrent gonococcal infection by antibiotics in nineteen patients showed them to be suffering from the classic non-specific urethritis. In each case differentiation from rheumatoid arthritis was made on clinical grounds. In a review of the literature it was noted that the radiological findings

had been reported only in isolated instances and this aspect was therefore studied in particular in the present series.

Radiologically, the most commonly affected areas were the feet, the hands, and the sacro-iliac joints. Spinal changes typical of ankylosing spondylitis were found in six cases. The knees, though often clinically affected, rarely showed radiological involvement. The time of appearance of radiological changes was variable. In some cases such changes were evident in the first few weeks or months, being preceded only by periarticular thickening around the small joints of the feet and hands, while in others radiological signs did not develop at all in the course of several years. Erosions of the articular surfaces of the affected joints were common and were invariably accompanied by narrowing of the joint space which might progress to disorganization and subluxation. Periosteal new bone formation of various types was a striking feature in many cases, affecting especially the short bones. Flattening of the arches of the feet, with which dislocation of the metatarso-phalangeal joints was usually associated, was seen in several cases. The radiological differentiation of Reiter's syndrome from rheumatoid arthritis may not be radiologically possible, and the authors consider that in atypical cases of the latter condition in males evidence of urogenital infection should be sought.

R. O. Murray.

**Radiological Aspects of Reiter's Syndrome ("Venereal" Arthritis).** REYNOLDS, D. F., and CSOKA, G. W. (1958). *J. Fac. Radiol. (Lond.)*, 9, 44. 12 figs, 7 refs.

Radiographs from 58 male and two female patients with Reiter's syndrome out of a total of 185 seen at St. Mary's Hospital, London, were studied in an attempt to assess the radiological features of the condition. The triad of arthritis, urethritis, and conjunctivitis was present in 35 cases, the last feature being absent in 25. The radiological findings were the same in both groups. Clinically, the arthritis is most common in the distal joints of the lower extremity, the knee and ankle being involved in over 70 per cent. of the whole series of 185 cases, the hand and wrist in over 55 per cent., and the sacro-iliac joints in 9 per cent. A valuable summary of the differences between Reiter's syndrome and rheumatoid arthritis is given.

Radiologically, in the acute stage the affected joints showed periarticular thickening and localized bony rarefaction. Swelling of tendons, particularly the tendo achillis and the patellar tendon, could be seen and was regarded as a differentiating feature from rheumatoid arthritis. Periosteal new bone formation was demonstrated in 27 per cent. of cases around the small bones of the feet. Plantar spur formation on the os calcis was sometimes observed after an initial stage of erosion in association with a plantar fasciitis. However, some of the spurs were similar to those seen frequently in routine radiography, and caution is necessary in ascribing them to the disease process. In the chronic stage extensive new bone formation often occurred on the plantar aspect of the os calcis, frequently bilaterally and foot deformities

develop subsequently in some cases. If the arthritis was persistent the joint space might become narrowed, serial films showing the development of marginal erosions. In the course of healing such erosions were likely to develop a sclerosed edge, but permanent defects were left. The sacro-iliac joints of 34 patients were investigated; pitting of the articular surfaces and subarticular sclerosis were observed in eleven, but complete ankylosis was not seen. In only one of these cases were spinal changes observed. Other changes included true bony ankylosis, mainly in the small joints of the feet, in eight cases, and the Pellegrini-Stieda type of calcification in the knee in two.

The authors consider that this syndrome is not rare and should be considered in the differential diagnosis of polyarthritis in the male.

R. O. Murray.

#### Phenolic Compounds in Chemotherapy of Rheumatic Fever.

CLARKE, N. E., CLARKE, C. N., and MOSHER, R. E. (1958). *Amer. J. med. Sci.*, **235**, 7. 23 refs.

By adopting the principle of investigating chemicals related to one manifesting therapeutic activity, we sought an improved treatment for rheumatic fever. We tested compounds related to salicylic acid or the diphenols gentisic acid, protocatechuic acid, pyrocatechuic acid, beta resorcylic acid, gamma resorcylic acid, and the triphenols phloroglucinol carboxylic and 2:3:6-trihydroxy benzoic acids.

Increased antirheumatic potency was found in phenolic compounds with double chelate rings and superior antirheumatic qualities were associated with a second or third hydroxyl group in the 3 position on the benzene ring. The compounds that had double chelate rings or single chelate ring and hydroxyl group in the 3 position did not generate usual urinary changes associated with detoxication. Phenolic compounds produce some changes that are associated with antirheumatic adrenal hormones but differed by producing relative increases in circulating lymphocyte cells and decreasing the urinary excretion of 17-ketosteroids.

The high antirheumatic potency of double chelating phenols supports the importance of antirheumatic metabolites in salicylic acid therapy. The compound 2:3:6-trihydroxy benzoic acid has the highest potency but is non-toxic and when used early in the first attack of rheumatic fever seemed to prevent damage to the heart.

Certain phenolic compounds have a normalizing or saving action in rheumatic fever thereby permitting their direct utilization by the body.—[Authors' summary.]

#### Genito-urinary Focus in Rheumatic Disorder in the Male.

[In English.] DOMEIJ, B., GIERTZ, G., OLHAGEN, B., and ROMANUS, R. (1958). *Acta chir. scand.*, **115**, 1. 1 fig., 7 refs.

In a study of the incidence of prostatic-vesiculitis in various rheumatic diseases, carried out at Karolinska Sjukhuset, Stockholm, all male patients (190) admitted to the rheumatological clinic over a period of 12 months were examined by palpation of the prostate gland and

seminal vesicles, and by cytological and bacteriological examination of expressed secretions. The criteria for prostatitis were:

- (1) the detection by palpation of a pathological condition of the vesicles;
- (2) the presence in expressed fluid of more than twenty leucocytes per high-power field.

In the majority of cases culture of the secretion showed either no growth, or the normal flora of the male urethra.

In a control group of 66 patients subjected to the same examination evidence of prostatic-vesiculitis was found in 33 per cent. In the rheumatic group, of 73 patients with ankylosing spondylitis 71 (91 per cent.) had chronic inflammation of the prostate and vesicles, while of 61 patients with pronounced chronic rheumatoid arthritis positive results were found in 35 (58 per cent.). Apart from three cases of typical Reiter's syndrome the series included forty patients in whom rheumatic symptoms first appeared some weeks, up to 2 months, after a specific or non-specific urethritis. Among these patients, who presented some of the clinical features of Reiter's syndrome, evidence of prostatic-vesiculitis was obtained in 34 (83 per cent.). The aetiological significance of these observations is discussed.

Kenneth Stone.

#### Salicylates and Gastric Haemorrhage. I. Occult Bleeding. II. Manifest Bleeding. LANGE, H. F. (1957). *Gastroenterology*, **33**, 770 and 778. 32 refs.

Much has been written on the tendency for acetylsalicylic acid (aspirin) to cause localized gastric erosion and subsequent haemorrhage. The author reports, from Ullevål Hospital, Oslo, the results of an extensive investigation into this subject, the first part of which was concerned with the incidence of occult bleeding from the gastro-intestinal tract in 110 arthritic patients receiving salicylate therapy. The patients were divided into six different groups which were given five different types of salicylate preparation, and the faeces were examined by benzidine test for occult blood before (in 50 cases), during therapy (in all 101 cases), and after therapy (in 48 cases), which lasted for a mean period of 21 days. This test gave a positive result on 298 (38 per cent.) of 783 faecal specimens examined during treatment, and on 37 out of 103 specimens examined 5 days after the end of treatment. There did not appear to be any marked difference in the results produced by different preparations of salicylates, except that one which had an effective enteric coating was shown, as expected, to be the least irritating. It was notable that calcium salicylate and a salicylo-glycine preparation (which are alleged to have the property of rapid and fine dispersion) both produced positive occult-blood reactions. In general the number of positive reactions was significantly reduced if the tablets were taken immediately after meals. The use of enteric coating also tended to reduce the incidence of occult bleeding, but there is some doubt as to whether this permits satisfactory absorption and the attainment of an adequate serum level of salicylate.

In the second part of the study an attempt was made to determine the part played by salicylates in the causation

of manifest bleeding from the gastro-intestinal tract in 96 patients admitted to hospital because of haematemesis or melaena, of whom 45 had been taking salicylates for a variety of stated reasons and 51 had not. These 96, together with a control group of 31 patients admitted with peptic ulceration but without bleeding, were studied in three groups. Of the 31 control patients in Group 1, six (19 per cent.) gave a history of having taken salicylates shortly before admission. Group 2 consisted of 62 of the patients with bleeding in whom, following the appearance of gastro-intestinal haemorrhage, radiological examination revealed organic disease; of these, 24 (37 per cent.) had taken salicylates shortly before the bleeding episode. Of the 34 patients in Group 3, in whom the x-ray findings following haematemesis or melaena were negative, nineteen (56 per cent.) gave a history of taking salicylate shortly before admission. The differences between the numbers taking salicylates in Groups 1 and 3 and in Groups 1 and 2 were statistically significant. The author therefore concludes that the salicylates were a significant factor in provoking gastro-intestinal haemorrhage, and notes that this effect was particularly marked in the elderly.

J. N. Harris-Jones.

**Possible Basis for the Anti-Inflammatory Activity of Salicylates and Other Non-Hormonal Antirheumatic Drugs.** ADAMS, S. S., and COBB, R. (1958). *Nature (Lond.)*, **181**, 773. 11 refs.

**Relationship between Infective Rheumatism, Rheumatic Fever, and Rheumatoid Arthritis.** (Rapports entre les rhumatismes infectieux, la maladie de Bouillaud et la polyarthrite chronique évolutive.) ROBECCHI, A. (1958). *J. belge Med. phys. Rhum.*, **13**, 127.

**Rubella Arthritis: Report of Cases studied by Latex Tests.** JOHNSON, R. E., and HALL, A. P. (1958). *New Engl. J. Med.*, **258**, 743. 16 refs.

**Case of Caplan's Syndrome in a Boiler-Scaler.** CAMPBELL, J. A. (1958). *Thorax*, **13**, 177. 4 figs, 3 refs.

**Trauma in the Aetiology and Pathogenesis of Primary Rheumatism (Acute and Chronic).** (Il trauma nell'etiopatogenesi del reumatismo primario.) SCHIAVETTI, L., and GOSPODINOFF, A. (1958). *Policlinico, Sez. prat.*, **65**, 1015.

**Phenylbutazone Metabolites: Antirheumatic, Sodium-Retaining, and Uricosuric Effects in Man.** YÜ, T. F., BURNS, J. J., PATON, B. C., GUTMAN, A. B., and BRODIE, B. B. (1958). *J. Pharmacol.*, **123**, 63. 1 fig., 10 refs.

**Carpal Canal Syndrome.** (Le syndrome du canal carpien.) LAMBERT, P. (1958). *Rhumatologie*, **10**, 86. 29 refs.

**Serum Protein and Glycoprotein Alteration in Swine with Experimental Arthritis.** SHETTLAR, M. R., SHETTLAR, C. L., PAYNE, R. W., NEHER, G. M., and SWENSON, C. B. (1958). *Proc. Soc. exp. Biol. (N.Y.)*, **98**, 254. 10 refs.

**Rheumatoid Lung Changes associated with Asbestosis.** RICKARDS, A. G., and BARRETT, G. M. (1958). *Thorax*, **13**, 185. 7 figs, 36 refs.

**Reaction with Lugol's Solution in Rheumatic Diseases.** (Reakce s lugolovým roztokem u revmatických chorob.) MARŠÍKOVÁ, L., VOJTIŠEK, O., ŠULC, M., and KLAS, J. (1958). *Čas. Lék. čes.*, **97**, 909. 15 refs.

**Fluoridation of Public Water Supplies and Its Relation to Musculoskeletal Diseases.** STEINBERG, C. L., GARDNER, D. E., SMITH, F. A., and HODGE, H. C. (1958). *New Engl. J. Med.*, **258**, 322. 12 refs.

### Disk Syndrome

**Cervical Spine. An Anatomicopathological Study of 70 Specimens (Using a Special Technique) with Particular Reference to the Problem of Cervical Spondylosis.** PAYNE, E. E., and SPILLANE, J. D. (1957). *Brain*, **80**, 571. 19 figs, 35 refs.

The Gough-Wentworth technique for mounting large sections (400 to 600 $\mu$  thick) of entire organs on paper, which was originally devised to facilitate the study of pulmonary disease, was employed together with other methods by the present authors to investigate the normal anatomical features of the cervical spine and to discover the presence of any abnormalities due to ageing or disease which might be responsible for cervical spondylosis. The study was carried out at the Welsh National School of Medicine, Cardiff, on seventy cervical spines removed at routine necropsy on 56 male and 14 female patients, of whom 64 were over the age of 40. The findings are described in detail and profusely illustrated.

An important conclusion of the study was that cervical spondylosis is a degenerative process of unknown aetiology affecting the vertebral bodies and the intervertebral disks. The nuclei of the disks are nearly always partially displaced into the bodies of the adjoining vertebrae or through the annulus fibrosus. The cervical nerves may be kinked or compressed by ridges or projections formed on the anterior or lateral surface of the spinal canal or by changes within the intervertebral foramina. Reduction in the size of the spinal canal and resultant compression of the spinal arteries may lead to myelopathy in some cases. When indicated in treatment the cervical spine is best immobilized with the neck in slight flexion and the shin "tucked in".

L. Crome.

**Pharyngolaryngeal Disturbances due to Cervical Spondylosis.** LASKIEWICZ, A. (1958). *A.M.A. Arch. Otolaryng.*, **67**, 292. 5 figs, 30 refs.

Osteo-arthritic changes in the cervical vertebrae are very common. Schindel found such changes in 44.5 per cent. of heavy manual workers and in 34.5 per cent.



of mental workers and clerks. That these changes could cause symptoms in the throat was suggested by Pierre Marie some 60 years ago. Since then a variety of troubles has been attributed to this condition, varying from gross physical obstruction of the oesophagus by exostosis of the body of a vertebra to irritation of the lateral spinal roots by oedema of the surrounding meningeal sheaths.

The present author describes twelve cases, eleven in men and one in a woman, seen by him in London between 1943 and 1957. In seven of these inner ear troubles predominated and in five cases pharyngolaryngeal symptoms with remote neuralgic pains. It was considered that four of the cases were due to acute arthritis and eight to chronic degenerative changes with new bone formation within the vertebrae. The inner ear changes include deafness of cochlear type, tinnitus, and vertigo due to interference with the blood supply by irritation of the sympathetic plexus around the vertebral artery; the neuralgic pains were attributed to irritation of the periarterial sympathetic plexus in their course through the intervertebral foramina. Diagnosis was confirmed by laryngo-endoscopic examination, radiography, palpation of the spinal roots, and elicitation of crepitation on head movements. Treatment consisted in electrical massage of the posterior part of the neck, short-wave therapy, and friction with iodine oil. Immobilization by means of a plastic collar was also employed. If all these fail, paravertebral blocking of the sympathetic and parasympathetic pathways with 1 per cent. procaine may be tried.

F. W. Watkyn-Thomas.

**Cervical Diskography. Technique, Indications and Use in Diagnosis of Ruptured Cervical Disks.** CLOWARD, R. B. (1958). *Amer. J. Roentgenol.*, **79**, 563. 9 figs, 18 refs.

The author describes his technique of cervical diskography based on experience in 41 clinical cases seen over an 18-month period at Honolulu, Hawaii. In contradistinction to lumbar diskography, in which a posterior approach is used, the cervical nucleus pulposus is approached from an antero-lateral direction to avoid passing through the spinal cord. Under local anaesthesia, 0.2 to 0.5 ml. 50 per cent. "hupaque" or 70 per cent. "urokon" is injected.

The appearance of the diskogram in the three types of abnormality of cervical disks which may cause clinical symptoms are described:

- (1) In early rupture of the disk following trauma ("whiplash" injury), where the plain radiograph shows a normal disk space, the diskogram demonstrates posterior herniation and often lateral extension of the nucleus pulposus.
- (2) In chronic disk degeneration with narrowing of disk spacing and osteophyte formation, although the diagnosis is obvious from the symptomatology and the plain radiograph, the diskogram may often reveal a larger protrusion into the spinal canal than would be expected from inspection of the plain x-ray film or the myelogram only.

- (3) In massive disk protrusion, which often shows obstruction of the spinal canal on myelography and may be diagnosed as neoplasm of the cervical cord, the differential diagnosis may be made by diskography. On injection of the disk, most patients experience some pain, the distribution of which roughly corresponds to the neuralgia and is a valuable objective sign in helping to locate the disk from which symptoms originate; it also provides differential diagnosis from neuralgias due to the scalenus anterior syndrome and other lower brachial plexus or peripheral nerve lesions.

Both on theoretical grounds and on his experience during 6 years of lumbar diskography performed on over 400 patients, the author considers that a normal disk cannot be injured by diskography if properly performed. Cervical diskography also appears in some cases to offer more diagnostic information than the myelogram. Thus, in postero-lateral herniation where the protrusion does not impinge on the dura, and in small central posterior herniations, the myelogram may show a normal appearance, but the diskogram will demonstrate the lesion.

Michael C. Winter.

**Cervical Disk Lesions.** ODOM, G. L., FINNEY, W., and WOODHALL, B. (1958). *J. Amer. med. Ass.*, **166**, 23. 12 refs.

In this paper from Duke University School of Medicine and Hospital, Durham, N. Carolina, are reviewed 246 cases of surgically verified cervical intervertebral disk lesions. These were causing either root or cord compression, and included both true protrusions composed of intervertebral disk tissue and bony spurs associated with degenerative changes in the cervical joints. Of the 221 lateral lesions with root involvement, 175 were disk protrusions and 46 bony spurs, the average age of patients in the former group being 43 years and in the latter 49 years. Both types of lesion occurred at the interval between either the 5th and 6th or 6th and 7th cervical vertebrae in 90 per cent. of the cases. The symptomatology was of the now well recognized type. A motor defect was present in 204 (93 per cent.) of the 221 cases, and in lesions at the two common sites involved the triceps much more frequently than the biceps or deltoid. A sensory defect occurred in 173 (78 per cent.) of the cases, and at the periphery affected the thumb with 6th-root involvement (C5-6 protrusion) and the index finger with 7th-root involvement.

Radiological abnormalities in the cervical spine were present in three-quarters of the cases, but were of no value in location, corresponding to the myelographic abnormality in only 30 per cent. of the cases. Myelography gave valuable information in almost all the cases of disk protrusion, but revealed the level of a foraminal spur in only eighteen out of 29 cases. The results of surgical treatment were considered excellent in 94 (57 per cent.) of the cases of disk protrusion and nineteen (45 per cent.) of those of foraminal spur, all of the remaining patients having residual symptoms of greater or less severity. There were five re-operations for recurrent



symptoms, and the only serious post-operative complication was due to cerebral anoxia occasioned by anaesthesia. There were no deaths in the series.

Of the 25 cases of medially placed lesions with cord compression, fourteen had disk protrusion and eleven cervical spondylosis. The protrusion occurred at the three lowest cervical disks in patients whose average age was 46. Pain was rarely a feature, and the picture was one of a progressive spastic paraparesis with later involvement of the arms. Myelography revealed the lesion in each case and again indicated that the changes shown on plain films are misleading. The results of surgical removal were classed as good in four cases, satisfactory in eight, and poor in two. In the cases of spondylosis the value of myelography was again apparent, and the results of surgery were classed as good or excellent in two cases, satisfactory in six, and poor in three. No attempt was made to excise either the lateral foraminal spurs or the transverse ridges in the cases of spondylosis with cord involvement.

[This is an excellent review of a large experience with cervical disk lesions. Although the authors consider that conservative treatment is indicated in the first instance, it is clear that only if the basis was quite markedly towards surgery could nearly 250 patients have had their cervical disk lesions surgically proved at one clinic in a 17-year period.] J. E. A. O'Connell.

### Gout

**Effect of Desacetylmethylcolchicine (Colcemide) in Acute Gouty Arthritis.** NEUSTADT, D. H. (1958). *Arthrit. and Rheum.*, 1, 91. 14 refs.

"Colcemid" (de-acetylmethylcolchicine; demecolcine) was given during a total of 22 acute attacks of gout to seventeen patients (13 men, 4 women) ranging in age from 17 to 68 years. A dose of 1 mg. was given hourly until the pain was relieved or gastro-intestinal symptoms supervened. Dramatic subjective improvement was noted by fifteen patients in a total of seventeen attacks, the total dose needed to produce clinical relief being usually 8 mg.

The gastro-intestinal side-effects observed were less severe than with colchicine. However, a warning is issued that, unlike colchicine, demecolcine may depress the bone marrow and cause granulocytopenia, and also that complete, though temporary, loss of hair is an occasional side-effect of the drug. G. S. Crockett.

**Protracted Uricosuric Therapy in Tophaceous Gout.** GUTMAN, A. B., and YÜ, T. F. (1957). *Lancet*, 2, 1258. 2 figs, 15 refs.

The authors report their experience at Mount Sinai Hospital (Columbia University), New York, in the treatment of 82 patients with tophaceous gout who received uricosuric agents continuously for periods varying from 6 months to 7 years. No new tophi appeared during treatment, in 36 cases existing tophi either disappeared or were considerably reduced, in 31 there was a moderate

or slight reduction in size of the tophi, and in fifteen no change was observed; in eleven of this last group, however, treatment had been given for less than one year. Of 52 cases of chronic gouty arthritis, there was complete resolution in 37 and improvement in a further twelve. The patients whose tophi showed little change fell into two groups—those with an inadequate uricosuric response because of impaired renal function, insufficient dosage owing to drug intolerance or precipitation of renal colic, or "immoderation in diet"; and those with an adequate uricosuric response but in whom the remaining tophaceous material was presumably inaccessible.

The following uricosuric agents were employed:

- (1) Salicylates, of which the daily dosage required is 5 g. or more, which inevitably produces salicylism.
- (2) Probenecid, which is much less toxic, only occasionally causing a rash or gastric distress, but has the disadvantages that it tends to precipitate acute attacks of gout, that it has no analgesic properties, and that in some cases, particularly when there is renal damage, it does not reduce the serum urate level satisfactorily. The dosage required ranged from 0.5 to 3 g. daily.
- (3) Two analogues of phenylbutazone—G-25671, which contains a phenylthioethyl group in place of the butyl side-chain, and G-28315, its sulphoxide. Both these drugs, especially G-28315, were more effective uricosuric agents than probenecid, while G-25671 also has mild analgesic properties; so far neither has caused any major side-effects. The required dosage of G-25671 was 0.4 to 2 g. and G-28315 0.46 to 0.6 g. daily. There were individual variations in the response to treatment, and the optimum dosage of each drug was best established by direct measurement of its uricosuric effect, the aim being to produce an increase by 50 to 100 per cent. in the urinary output of urate and a reduction of the serum uric acid level to 6 mg. per 100 ml. It was, of course, not always possible to achieve either goal, particularly in the presence of renal damage.

The authors prefer not to start uricosuric therapy until there are early indications of tophus formation or joint stiffness, while the duration of treatment must depend on the magnitude of the mobilization of urate achieved. Uricosuric agents have no place in the treatment of acute attacks, and the authors' experience does not support the claim that probenecid acts as a prophylactic against acute attacks, although colchicine is of some value for this purpose. They consider it doubtful whether uricosuric agents should be used in cases of non-tophaceous gout simply to reduce the serum uric acid level; in patients with a previous history of renal colic or renal stones there is some danger of precipitating further trouble of this nature, and if uricosuric therapy is indicated in such cases an adequate fluid intake should be secured and the smallest effective dosage of the agent should be employed. B. M. Ansell.

**Mechanism of Overproduction of Uric Acid in Patients with Primary Gout.** WYNGAARDEN, J. B., BLAIR, A. E., and HILLEY, L. (1958). *J. clin. Invest.*, **37**, 579. 10 figs, bibl.

Using glycine- $^{15}\text{N}$ , in both large and tracer doses, previous workers have shown that the hyperuricaemia in primary gout is due to the overproduction of uric acid from glycine and other small molecules. To investigate the mechanism by which this occurs the present authors, working at Duke University School of Medicine, Durham, N. Carolina, and the National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland, have incorporated glycine- $^{14}\text{C}$  into various urinary purine bases and compared the enrichment patterns with those of uric acid. The subjects consisted of three patients with primary gout, one with polycythaemia vera and secondary gout, and one with myeloid metaplasia, together with four controls. After 5 days on a purine-poor diet, which was continued throughout the study, glycine- $^{14}\text{C}$  was given by mouth and 24-hour urine collections were begun. Uric acid was estimated spectrophotometrically. The urinary purines were precipitated copper, redissolved in hydrochloric acid, and after further purification placed on an analytical column of "dowex-50-H+" resin, from which it was possible to elute hypoxanthine, xanthine, adenine, guanine, 7-methyl-guanine, and 7-methyl-8-hydroxyguanine. The highly labelled purine bases hypoxanthine and guanine, which were present within hours, were thought to be due to cleavage of newly formed nucleotides and occurred in all subjects. In the patients with myeloid metaplasia the direct pathway involving the nucleotides of guanine and adenine showed a significant increase. In primary gout most of the labelled urate was thought to result from nucleotide cleavage, which occurred more quantitatively and possibly more quickly than in the controls, but as the labelling of guanine was also increased as compared with the controls there appeared to be increased formation of nucleotides as well.

The authors conclude that in man uric acid may arise from nucleotide cleavage as well as catabolism of nucleic acids, and the derangement in gout is probably complex, involving several compounds at nucleotide level. It is suggested that it may well be a defect in the regulation of urate production rather than the absence of any specific reaction.

B. M. Ansell.

**Intravenous Colchicine in the Treatment of Gout.** (Colchicine intravenosa en el tratamiento de la gota.) LOSADA L. M., LOSADA L. A., and FRANCE S. O. (1958). *Arch. argent. Reum.*, **21**, 23. 1 fig., 9 refs.

**Treatment of Acute Gouty Arthritis with Demecolcine.** COLSKY, J., WALLACE, S., and BANOWITZ, M. M. (1957). *A.M.A. Arch. intern. Med.*, **100**, 765. 5 figs, 14 refs.

# Pararheumatic (Collagen) Disease

**Simple Indirect L.E.-cell Test with Increased Sensitivity.** [In English.] KIEVITS, J. H., and SCHUIT, H. R. E. (1957). *Vox Sang. (Basel)*, **2**, 288. 13 refs.

In this paper from University Hospital, Leiden, the authors describe a new indirect L.E.-cell test claimed to be more sensitive than the tests hitherto employed. About 0.5 ml. of the serum being tested is added to an equal volume of fragmented and washed blood clot obtained from normal blood. The mixture is agitated at intervals for 20 minutes at room temperature, centrifuged, the buffy coat removed, and centrifuged again. This second buffy layer is then removed and smears made in the usual manner with Giemsa stain. The slide with the greatest cell density is used for counting the number of L.E. cells.

The sensitivity of the test is stated to be greater than that of other indirect tests, but still does not equal that of the very sensitive direct clotted-blood technique described by Zimmer and Hargraves (*Proc. Mayo Clin.*, 1952, **27**, 424). The authors' method also has the slight disadvantage that the blood groups of the leucocyte donor and the patient must be compatible.

E. G. Rees.

**Serum Glutamic Oxalacetic Transaminase in Dermatomyositis.** MORAGAS, J. M. DE, PERRY, H. O., and FLEISHER, G. A. (1957). *J. Amer. med. Ass.*, **165**, 1936. 1 fig., 10 refs.

The serum glutamic oxalacetic transaminase level in dogs is known to be raised in the presence of damage to the myocardium, liver, and brain. A similar increase has been observed following injury, however caused, to skeletal muscle. At the Mayo Clinic an attempt was made to correlate the serum transaminase level with the clinical state of seventeen patients with dermatomyositis. The diagnosis of the disease was based on the clinical findings, the results of electromyography, and, in some cases, examination of skin and muscle biopsy specimens. [The findings are not stated.] In three clinically quiescent cases of dermatomyositis the serum transaminase level was normal (the normal being established in fifty controls) while in most of the fourteen active cases the level was raised. The serum transaminase level was also determined in a few patients suffering from other conditions. In two out of four cases of systemic lupus erythematosus the level was high, while in a few cases of discoid lupus erythematosus, acrosclerosis, and some other skin conditions it fell within the normal range.

In four cases of dermatomyositis in which serial determinations were carried out there was an indication that the transaminase level fell with clinical improvement during administration of cortisone.

G. Loewi.

**Progressive Systemic Sclerosis (or Visceral Scleroderma). Review of the Literature and Report of Cases.** [Monograph.] ORABONA, M. L., and ALBANO, O. (1958). *Acta med. scand.*, **160**, Suppl. 333. 53 figs, bibl.

**Morbid Anatomy and Histology of Disseminated Lupus Erythematosus.** (Pathologische anatomie en histologie van lupus erythematosus generalisatus.) UNNIK, J. A. M. VAN (1958). *Ned. T. Geneesk.*, **102**, 978. 32 refs.

**Scleroderma and Dermatomyositis.** (Escleroderma-dermatomyositis.) BORDA, J. M. (1957). *Pren. méd. argent.*, **44**, 1983.

**Incidence of Disseminated Lupus Erythematosus. Follow-up Studies indicating Increased Frequency.** SVANBORG, A., and SÖLVELL, L. (1957). *J. Amer. med. Ass.*, **165**, 1126. 9 refs.

**Phase Contrast and Interferometric Microscopy of the L.E. Cell Phenomenon.** RIFKIND, R. A., and GODMAN, G. C. (1957). *J. exp. Med.*, **106**, 607. 22 figs, 31 refs.

**Antigenic Constituents of the Neutrophilic Leukocyte with Special Reference to the L.E. Phenomenon.** [In English.] MIESCHER, P. (1957). *Vox Sang. (Basel)*, **2**, 145. 5 figs, 36 refs.

**Scleroderma in Gold-miners on the Witwatersrand, with Particular Reference to Pulmonary Manifestations.** [In English.] ERASMUS, L. D. (1957). *S. Afr. J. Lab. clin. Med.*, **3**, 209. 5 figs, 29 refs.

**Scleroderma of the Gastro-intestinal Tract. A Review.** GOLDGRABER, M. B., and KIRSNER, J. B. (1957). *A.M.A. Arch. Path.*, **64**, 255. 5 figs, 41 refs.

**Rationale for the Treatment of Lupus Erythematosus with Anti-malarials.** MCCHESENEY, E. W., NACHOD, F. C., and TANTER, M. L. (1957). *J. invest. Derm.*, **29**, 97. 2 figs, 39 refs.

### General Pathology

**Localization and Binding of Serum Proteins in the Glomeruli of Kidney Biopsies in Disseminated Lupus Erythematosus and Glomerulonephritis.** TAFT, L. I., DINEEN, J. K., and MACKAY, I. R. (1958). *Aust. Ann. Med.*, **7**, 5. 13 figs, 14 refs.

In this paper from the Walter and Eliza Hall Institute and the Royal Melbourne Hospital a further application of the fluorescent-antibody technique is described. Sections of the renal biopsy specimens from 24 patients (nine suffering from diffuse lupus erythematosus, one from lupoid hepatitis, and fourteen from a variety of other kidney diseases) were treated with fluorescent rabbit anti-human  $\gamma$ -globulin and compared with seven normal control sections similarly treated. Coupling of the fluorescent antibody in the capillaries of the glomerulus, was observed in seven cases of lupus erythematosus and one of progressive glomerulonephritis, and to a lesser degree in one case of diabetic nephropathy. Technical difficulties resulted in the antibody showing some cross-reactions with human albumin as well as  $\gamma$ -globulin. The

absence of protein staining in other parts of the section suggested to the authors that the protein demonstrated by this technique in the glomerulus was tightly bound to the tissue, whereas the remainder had been washed out during the staining procedure. They therefore suggest that this binding of serum protein represents an antigen-antibody reaction, though it may, of course, be due to secondary adsorption of plasma by a damaged capillary wall.

G. J. Cunningham.

**Lesions of Lymph Nodes in Rheumatoid Disease and in Disseminated Lupus Erythematosus.** CRUICKSHANK, B. (1958). *Scot. med. J.*, **3**, 110. 13 figs, 23 refs.

In this paper from the Royal Infirmary, Glasgow, the lesions found in the lymph nodes in twenty cases of rheumatoid arthritis and twelve cases of diffuse lupus erythematosus are described and contrasted with those seen in follicular lymphoma. In two cases of rheumatoid arthritis the history was normal. In another thirteen cases the principal change was follicular hyperplasia, in two of them combined with sinus catarrh. The general architecture of the lymph nodes was preserved, whereas in the cases of follicular lymphoma studied for comparison it has become distorted. Follicles were increased in size and number in both conditions. In rheumatoid arthritis phagocytic histiocytes, plasma cells, and hyaline eosinophil material were present, but these features were rare or absent in follicular lymphoma. In three other cases of rheumatoid arthritis the principal change was sinus catarrh; sinuses were enlarged and there was proliferation of littoral cells. A further case showed diffuse histiocytic hyperplasia, and another diffuse lymphocytic hyperplasia. In all the cases of rheumatoid arthritis the lymph-node changes appeared to be systemic manifestations without definite localization in relation to joints or other affected organs.

All the cases of lupus erythematosus had lymph-node changes. Only one showed follicular hyperplasia, while nine had sinus catarrh. In five the medullary tissue contained large numbers of plasma cells. Hyaline material similar to that present in rheumatoid arthritis was found in one case, and haematoxylin bodies in another.

G. Loewi.

**Streptococcal Antibodies in Rheumatic Diseases.** (Les anticorps streptococciques dans les maladies rhumatismales.) RAVAUULT, P., VIGNON, G., and VIAL, J. (1958). *Rev. lyon. Med.*, **7**, 127.

As a further contribution to the diagnosis of rheumatic diseases—this term being used in the widest sense—the authors present the results of 671 determinations of antistreptolysin-O titre, antistreptohyaluronidase, and antistreptokinase in cases of "rheumatism" in both adults and children seen at various hospitals in Lyons; on 472 occasions all three antibodies were estimated simultaneously. The techniques employed are described and significant levels defined. A simultaneous rise in the level of at least two of the antibodies was regarded as a "positive response". The possible sources of error in performing the estimations are discussed.

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Of 104 normal subjects and 92 patients with non-rheumatic diseases the antibody levels were normal in over 80 per cent., and less than 9 per cent. showed a positive response as defined by the authors. Of 177 patients with acute or subacute rheumatic fever with carditis a positive response was found in 60 per cent., and normal levels in 16 per cent. When carditis was absent (127 patients), the incidence of positive responses ranged from 35 to 55 per cent. normal levels occurring in about 30 per cent. of the patients. In other forms of rheumatism normal levels were found in 85 per cent. and a positive response in from 0 to 14 per cent. of cases. In all groups the antistreptolysin-O titre rose more readily than the other values. The authors conclude that estimation of more than one streptococcal antibody level is of considerable value in the differential diagnosis of rheumatic fever from other forms of rheumatism.

David Friedberg.

**Agglutination of Collodion Particles sensitized with Gamma Globulin in Rheumatoid Arthritis.** (Agglutination der mit Gamma-Globulin sensibilisierten Kollodiumteilchen bei der chronischen Polyarthritis.) ZAVÁZAL, V. (1958). *Z. Rheumaforsch.*, 17, 41. 1 fig., 20 refs.

In this study, reported from the Institute of Immunology, Pilsen, Czechoslovakia, it was shown that collodion particles coated with normal human gamma globulin were agglutinated in 80 per cent. of 137 cases of rheumatoid arthritis. This was compared with the differential haemagglutination test (modification of Svartz) which gave 83 per cent. positive results in the same case material. With the collodion particles, however, much higher titres were obtained in the cases of rheumatoid arthritis, and also fewer false positive results in a normal control group than with the differential agglutination test. In a third group of forty cases of miscellaneous joint disorders other than rheumatoid arthritis, only four positive results were recorded with the collodion method against nineteen with the haemagglutination test. It appears therefore that the collodion-particle method is more sensitive and more specific in the diagnosis of rheumatoid arthritis than the differential haemagglutination test.

G. W. Csonka.

**Differences in the Fine Structure of Collagen and Reticulin as revealed by the Polarizing Microscope.** BREWER, D. B. (1957). *J. Path. Bact.*, 74, 371. 4 figs, 23 refs.

Under the polarizing microscope collagen from a variety of human and rat sources was found, in investigations here reported from the University of Birmingham, to have positive form and positive intrinsic birefringence, suggesting that it is made up of small particles and that the molecules in the particles are arranged in the long axis of the fibre. Different effects were observed when collagen was stained with different dyes. Toluidine blue and eosin behaved in opposite fashion, suggesting that the acidic and basic side-chains of collagen play an important role in its combination with dyes. Examination of stained collagen demonstrated that the dyes, whether acidic or basic, combined with orientated side-

chains, but the direction of the orientation could not be decided.

Reticulin from many human and rat sources also showed positive form, but with negative intrinsic birefringence. Unlike collagen, reticulin when stained did not show anomalous colours. The birefringence was less in frozen unfixed than in frozen formalin-fixed material. Treatment of unfixed sections of reticulin with enzymes destroyed its positive staining by the periodic-acid-Schiff technique.

The effect of treatment with tannic acid on collagen was to convert the intrinsic birefringence from positive to negative. The positive-form birefringence of both collagen and reticulin suggests that they are made up of longitudinally arranged particles. In collagen, however, the side-chains are orientated and free to combine with acidic or basic dyes, whereas in reticulin side-chains, if present, are not free or may contain an additional component.

R. E. Tunbridge.

**Complement Fixation with Cell Nuclei and DNA in Lupus Erythematosus.** ROBBINS, W. C., HOLMAN, H. R., DEICHER, H., and KUNKEL, H. G. (1957). *Proc. Soc. exp. Biol. (N.Y.)*, 96, 575. 7 refs.

Experiments were carried out at the Rockefeller Institute for Medical Research, New York, to see whether complement is removed in the reaction between the lupus erythematosus (L.E.) factor in the serum in cases of the disease and cell nuclei or deoxyribonucleic acid (DNA). The nuclei and DNA were obtained from a variety of sources and gave almost identical results. Complement fixation occurred in tests on nuclei with 22 out of thirty sera from cases of systemic lupus erythematosus. It was found that there was close correlation between the potency of the serum, as judged by the L.E. test, and its ability to fix complement. No significant complement fixation occurred with sera from normal subjects or from patients with rheumatoid arthritis, hepatic cirrhosis, or other diseases associated with hypergammaglobulinaemia.

The authors made the unexpected finding that complement fixation with cell nuclei was independent of that with DNA and vice versa, and conclude that two distinct serum factors must be present. These observations provide further evidence that antibodies to DNA and other nuclear components exist in the serum of patients with systemic lupus erythematosus.

E. G. Rees.

**Latex-Fixation Test using Whole Serum and an Euglobulin Fraction in Various Arthritic Disorders.** OLSEN, C. R., and RANTZ, L. A. (1958). *Arthrit. and Rheum.*, 1, 54. 24 refs.

This paper from Stanford University School of Medicine, San Francisco, reports further experience in the evaluation of diagnostic tests for rheumatoid arthritis. The latex-fixation test of Singer and Plotz (*Amer. J. Med.*, 1956, 21, 888; *Abstr. Wld Med.*, 1957, 22, 50) [designated the F.II. L.P. test by the Arthritis and Rheumatism Foundation] was carried out on 113 specimens of serum from various sources, a commercial preparation of poliomyelitis immune human globulin serving as the source of  $\gamma$ -globulin instead of Cohn's Fraction II as in the origina



method. In 23 (56 per cent.) of 41 cases of "definite" rheumatoid arthritis a positive result (agglutination to a titre of 1 : 160 or more) was obtained, while in 25 (92.6 per cent.) of 27 cases of "probable" and all of seventeen cases of "possible" rheumatoid arthritis the result was negative. [In cases of "definite" or classic rheumatoid arthritis Singer and Plotz obtained 71.3 per cent. positive results and Hartfeld and others, 68.2 per cent.] A further refinement was achieved by applying the test to the euglobulin fraction isolated from the serum by the Ziff dialysis technique. Of seventeen of the sera from cases of "definite" rheumatoid arthritis which had given a negative result in the original test, eleven then gave a positive reaction, the proportion of positive results being increased to 85 per cent. of the "probable" cases which had given the majority of negative results, 30 per cent. became positive when retested by the modified technique. No positive reactions were obtained by the euglobulin method with the sera from "possible" cases or with sera from 23 cases of other types of arthritis or from healthy persons. A higher proportion of positive results was obtained in cases of "definite" rheumatoid arthritis occurring in males than in females. Correlation between positivity of the reaction and the presence of other features of rheumatoid arthritis was highest in the case of typical radiological changes and subcutaneous nodules, a positive reaction being obtained in 91.7 per cent. of patients with the latter and 81.3 per cent. of patients with the former [but the two groups contained only twelve and sixteen patients respectively].

Harry Coke.

**Leucocyte Disk Method for L.E. Cell Test in Serum and Serum Fractions.** FALLET, G. H., and ZIFF, M. (1958). *Arthrit. and Rheum.*, 1, 70. 12 refs.

A simplified method of testing serum and serum fractions for L.E.-cell activity is described in this paper from New York University College of Medicine. Disks of living polymorphonuclear leucocytes were obtained by allowing drops of blood to remain in contact with glass slides for 20 minutes in a moist warm chamber. Immediate exposure of these leucocytes to serum from thirty patients with systemic lupus erythematosus was followed by the formation of L.E. cells in 29 out of the thirty cases. Positive results in this test were also obtained with sera from eight out of 76 patients with rheumatoid arthritis; the results with sera from 81 control cases, however, were negative. The method has been used for testing serum protein fractions for the presence of L.E. factor. It is particularly suitable for studying stages in L.E. transformation because it can be carried out rapidly and little manipulation is required.

E. G. Rees.

**Ecologic Studies of Rheumatic Fever and Rheumatic Heart Disease. I. Procedure for isolating Beta Hemolytic Streptococci.** SCHAUB, I. G., MAZEIKA, I., LEE, R., DUNN, M. T., LACHAINE, R. A., and PRICE, W. H. (1958). *Amer. J. Hyg.*, 67, 46. 4 figs, 16 refs.

This paper from the Johns Hopkins University and

Hospital, Baltimore, describes a study of procedures for isolating  $\beta$ -haemolytic streptococci from throat swabs containing scanty numbers of these organisms. The swabs, taken from children with rheumatic fever or members of their families, were placed immediately into a tube of modified Pike's enrichment broth and sent straight to the laboratory. There the swab was removed and used to inoculate a sheep-blood-agar plate, after which it was returned to the tube and twirled vigorously in the broth to obtain as much material as possible in suspension. A tube of trypticase-soy-agar, melted and then cooled to 48 to 50° C., was then inoculated with a loopful of the enrichment-broth suspension, sheep blood added, and a pour-plate made. The enrichment broth was then incubated overnight and a subculture made on sheep-blood agar.

Of these three methods, the poured sheep-blood-agar plates gave the largest number of isolations of Group-A  $\beta$ -haemolytic streptococci. The results from the pour-plate method were 25 per cent. better, and from the enrichment-broth subculture 7 per cent. better, than those from the original plate, although each method gave some positive results with swabs which gave negative results by the other two. It was also found that when the plates were held at room temperature for 24 hours after the usual 18- to 24-hr period of incubation at 37° C. the number of positive isolations of Group-A streptococci was increased. Maxted's bacitracin method (which exploits the unusual sensitivity to this antibiotic of Group-A streptococci) was found to be of considerable value in the grouping of the strains isolated.

E. J. Holborow.

**Paper Electrophoresis of Human Synovial Fluid.** SANDSON, J., and HAMERMAN, D. (1958). *Proc. Soc. exp. Biol. (N.Y.)*, 98, 564. 1 fig., 13 refs.

**Contribution to the Morphology of Encapsulated Nerve Endings in the Joint Capsule and Periarticular Tissue.** [In English.] HROMADA, J., and POLÁČEK, P. (1958). *Acta anat. (Basel)*, 33, 187. 10 figs, 16 refs.

**Influence of Erythrocyte Factors on Their Sedimentation Rate.** PHEAR, D. (1957). *J. clin. Path.*, 10, 357. 1 fig., 16 refs.

**Leuco-Precipitins. II. Demonstration of a Precipitation Reaction between Leucocyte Extracts and the Serum of Patients with Disseminated Lupus Erythematosus.** (Leuco-precipitins. II. Mise en évidence d'une réaction de précipitation entre des extraits leucocytaires et le sérum de malades atteints de lupus érythémateux disséminé.) SELIGMANN, M. (1957). *Vox Sang. (Basel)*, 2, 270. 2 figs, 10 refs.

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**Effects on the Concentration of Potassium, Sodium, and Calcium in Exudates of Cortisone, Prednisone, Vitamin D<sub>3</sub>, Deoxycortone Acetate, Dihydrocortisone, and Digitoxin.** (Über die Beeinflussung des Kalium-, Natrium- und Kalziumgehaltes von Exsudaten durch Cortison, Prednison, Vitamin D<sub>3</sub>, Desoxycorticosteronacetat, Dihydrocortisone II und Digitoxin.) HOTOVY, R., and KAPFF, J. (1957). *Z. Rheumaforsch.*, **16**, 412.

**Electrophoretic Characteristics of the Haemagglutination Factor in Rheumatoid Arthritis (R.A.S. Factor).** (Elektrophoretisches Verhalten des hämagglutinationsfaktors der primär-chronischen polyarthrit (RAS-Faktor).) FRANGER, W., and SCHEIFFARTH, F. (1957). *Acta rheum. scand.*, **3**, 322. 1 fig., 16 refs.

**Acid-Soluble Phosphorus-Containing Fraction in Rheumatoid Arthritis Blood and Synovial Fluid. II.** [In English.] LÖVGREN, O., and LAAKSONEN-GIERER, T. (1957). *Acta rheum. scand.*, **3**, 313. 3 figs, 5 refs.

**Latex Fixation Test in Rheumatoid Arthritis.** (Der Latexfixationstest bei der primär chronischen Polyarthrit.) EGGHART, F., WIEDERMANN, G., and BRAUNSTEINER, H. (1957). *Wien. Z. inn. Med.*, **38**, 364. 12 refs.

**Antigenicity of Chondroitin Sulphate (23451).** QUINN, R. W., and CERRONI, R. (1957). *Proc. Soc. exp. Biol. (N.Y.)*, **96**, 268. 7 refs.

**Synovial Fluid Potassium.** MÄKINEN, P., and KULONEN, E. (1957). *Scand. J. clin. Lab. Invest.*, **9**, 388. 2 figs, 3 refs.

#### ACTH, Cortisone, and Other Steroids

**Mechanism of the Glucosuria produced by the Administration of Steroids with Glucocorticoid Activity.** FROESCH, E. R., WINEGRAD, A. I., RENOLD, A. E., and THORN, G. W. (1958). *J. clin. Invest.*, **37**, 524. 4 figs, 26 refs.

The mechanism by which glucocorticoids provoke an immediate glucosuria has been studied at the Peter Bent Brigham Hospital, Boston, in four healthy men aged 21 to 36 years. The glucose concentration in the blood and urine was measured by a specific glucose oxidase method, since it is known that only a fraction of the material measured by the sugar-reducing method or by polarization is in fact glucose. The studies were carried out after a 12-hour fast and during a water diuresis of 8 ml. urine per minute or more, and during continuous intravenous infusion of inulin to which glucose was added at the rates of 0.5, 1, and 1.5 g. per kg. body weight per hour. Prednisone (100 mg.) was given orally either at 12 and 3 hours before the start of the infusion, or 75 mg. was given daily for 4 days beforehand. In all the subjects the urinary excretion of glucose was increased, and this increase could be accounted for by a diminished glucose

tolerance or an increased glomerular filtration rate or both; maximal tubular reabsorption of glucose was unaffected. The degree of glucosuria was never increased when the glucose load was less than the maximal reabsorption rate.

The effect of cortisol (hydrocortisone) in a dose of 200 mg. infused over 10 hours in the absence of glucose loading, was also studied in two patients with renal glucosuria during a prolonged fast. The blood glucose level and urinary glucose excretion were both greatly increased. Increased glomerular filtration contributed to the glucosuria, but tubular reabsorptive capacity was unaltered. Increased hepatic gluconeogenesis is suggested in explanation of the findings.

Peter C. Williams.

**Cortisone Therapy prior to Surgical Intervention: Incidence and Effect on Adrenal Cortical Function.** GILLIES, A. J. (1958). *Anesth. Analg. curr. Res.*, **37**, 47. 8 refs.

In view of several recent reports of the development of adrenocortical insufficiency following stress (including surgical operation) in patients who had previously been receiving cortisone, the author questioned 2,490 patients undergoing operation at New Haven Hospital, Connecticut, regarding previous medication with steroids. Of these, 140 (5.6 per cent.) had had such therapy at some time, 76 of them for more than 2 weeks.

In such cases the author institutes the following regimen. Patients for elective operation are given 200 mg. cortisone intramuscularly on the day before operation, 100 mg. hydrocortisone intramuscularly at the time of premedication, and further doses of hydrocortisone (up to 200 mg.) during and at the end of the operation. Patients requiring emergency operation receive 400 mg. hydrocortisone intramuscularly before surgery and further doses during and at completion of the operation. In all cases cortisone medication is gradually withdrawn during the first five post-operative days. Of 39 of the above 76 patients so treated only one developed adrenal cortical insufficiency.

Mark Swerdlow.

**Production Rate of Cortisol in Man.** COPE, C. L., and BLACK, E. (1958). *Brit. med. J.*, **1**, 1020. 1 fig., 12 refs.

The method here described, from the Postgraduate Medical School of London, for estimating the production of hydrocortisone (cortisol) by the adrenal cortex depends upon noting the dilution of an oral dose of cortisol labelled with radioactive carbon (<sup>14</sup>C) in the urinary metabolites. The assumptions made and the sources of error in the method are fully discussed. In twelve patients convalescent from diseases unlikely to cause any adrenal stimulation, the mean recovery rate in a 24-hr sample of urine was 87 per cent. of the <sup>14</sup>C in the dose of radioactive cortisol given. The specific activity of the hydrocortisone metabolite, tetrahydrocortisone, in the urine of these patients indicated a daily output of hydrocortisone ranging from 4.9 to 27.9 mg. (mean 12.8 or 14.5 mg., according to the method of calculation). An experiment on five subjects showed that there was no significant difference in the mean estimated daily

output of hydrocortisone whether the radioactive cortisol was given by mouth or by intravenous injection.

In twelve persons given corticotrophin, 76.4 per cent. of administered  $^{14}\text{C}$  was recovered in 24 hours. In these conditions the estimated cortisol production varied from 21.8 to 257 mg. per day, with a mean of 127 or 99 mg. daily (according to the method of calculation). In four cases of hypoadrenalism due to Addison's disease or to hypopituitarism the mean recovery rate of  $^{14}\text{C}$  in 24-hr urine was 81 per cent., indicating a mean daily cortisol production of between 0.8 and 1 mg. The inhibition of cortisol production by prednisone can sometimes be measured by this method, provided that the metabolite prednisolone is first removed from the urine by extraction with chloroform. However, there is some evidence that tetrahydrocortisone may be among the metabolites of prednisone and consequently high figures may be obtained. In six patients with various active diseases the mean cortisol production ranged from 10 to 31.9 mg. daily, the mean production rate being between 18.1 and 22.2 mg. daily. In three cases of well marked hyperthyroidism the mean daily production of cortisol was between 21.9 and 25.3 mg., while in three patients with advanced hepatic cirrhosis but without ascites the mean values were between 6.7 and 9.5 mg. daily. A cortisol production rate of only 1 mg. daily was found in a pseudohermaphrodite.

P. A. Nasmyth.

**Salicylates and Adrenocortical Function in Man.** PETERSON, R. E., BLACK, R. L., and BUNIM, J. J. (1958). *Arthrit. and Rheum.*, 1, 29. 1 fig., 29 refs.

The effect of salicylates on adrenocortical function was investigated in five healthy subjects and four patients with rheumatoid arthritis. Single doses of 3.6 to 4.2 g. sodium salicylate given to fasting normal subjects did not alter the plasma hydrocortisone level, while in eight subjects who were given 3 to 6 g. sodium salicylate daily for 3 to 50 days the plasma hydrocortisone and corticosterone levels were not significantly changed. In three of these cases the urinary corticoid excretion fell during the period of treatment.

Administration of salicylate did not seem to alter the rate of metabolism of infused hydrocortisone or cortisone, or the rate of synthesis of hydrocortisone. In one patient in whom a satisfactory antirheumatic response had been achieved with salicylate, depression of adrenocortical function by means of fludrocortisone did not affect this response.

The results of these investigations lend no support to the theory that the salicylates owe their antirheumatic effect in man to their influence on pituitary-adrenal function.

G. S. Crockett.

**Acute Effect of Acetylsalicylic Acid in Man on the Plasma Concentration of Corticoids, the Corticotropin (ACTH) Response, and Urinary Steroid Excretion.** HERNDON, R. F., FREEMAN, S., WHEELER, J. X., and LESTINA, F. A. (1958). *A.M.A. Arch. intern. Med.*, 101, 623. 27 refs.

Investigations were carried out at the Chicago Wesley Memorial Hospital (Northwestern University Medical

School) and the Veterans Administration Hospital, Hines, Illinois, into the effects of high doses of acetylsalicylic acid (aspirin) on the plasma corticoid concentration and the urinary excretion of neutral 17-ketosteroids and corticosteroids. The 63 subjects included 26 with rheumatoid arthritis, but the results in this group did not differ substantially from those in the remainder, who were healthy adults. The diurnal variation in the plasma level of corticoids was first measured in the untreated subjects and then again in the same subjects after receiving 30 units ACTH (corticotrophin) intravenously over the first 6 hrs of the period of observation. After an interval of at least a week the same subjects were given 30 mg. aspirin per kg. body weight at 8 a.m., 10 a.m., and noon on two consecutive days, with corticotrophin as above on the second day, and the effects of this treatment on the plasma corticoid level, the response to corticotrophin, and the urinary excretion of neutral 17-ketosteroids and free and conjugated corticosteroids were measured.

Aspirin reduced the response of the plasma corticoid level to corticotrophin infusion, while increasing the urinary excretion of corticosteroids and reducing that of 17-ketosteroids. Given alone, however, aspirin increased the urinary excretion of 17-ketosteroids and corticosteroids, while producing a fall in the plasma corticoid level.

It would appear from these findings that aspirin may stimulate the pituitary gland, and that this stimulation depends on a reduction in the concentration of corticoids in the plasma. In this respect at least, therefore, it would seem illogical to give salicylates and cortisone together in the treatment of rheumatoid arthritis.

G. S. Crockett.

**Experimental Arthritis. III. Modifications of Acute Lesions in the Guinea-Pig by Corticotropin (ACTH) and Steroids.** JONES, R. S., and MAYNE, B. S. (1958). *A.M.A. Arch. Path.*, 65, 247. 39 refs.

Acute arthritis was induced in guinea-pigs by a single intravenous injection of  $\text{C}^{14}$ -labelled polysaccharide complex prepared from *Klebsiella pneumoniae*. This substance reaches the joints in high concentration and remains there for weeks. In autoradiographs the concentration of this compound appears to be greater in the synovial membrane than in the bone marrow of the same section. This suggests that the changes in the joints may be due to the selective localization of foreign polysaccharides. Groups of guinea-pigs received daily injections of cortisone, corticotropin, or related steroids for 7 days followed by the intravenous injection of the polysaccharide. The hormone treatment was continued for 2 or 7 days, after which time the animals were killed. In control animals not receiving hormones, three types of non-cellular material was identified in the joints after the polysaccharide injection:

- (1) Basophilic material. This substance was thought to be hyaluronic acid.
- (2) Eosinophilic PAS-positive material which had



the characteristics of hyaluronic acid and protein complex.

(3) Fibrin or fibrin-like material.

The synovial tissue showed proliferative changes. Corticotropin and cortisone alone or in combination led to a delayed increase in the basophilic material. The eosinophilic substance was increased by corticosterone and increased or unaffected by corticotropin and the other steroids. Cortisone decreased the synovial cell proliferation but not polypoid growth which followed the intravenous injection of the polysaccharide. Corticosterone had no effect on the cells, but nevertheless reduced the quantity of hyaluronic acid at 7 days. There may be a parallel between the steroid treatment of joint disease in man and in the guinea-pig. Corticotropin and cortisone increase the relative amount of hyaluronic acid without decreasing the protein material. Hyaluronic acid is a hydrophilic, colloidal, anionic polyelectrolyte which binds cationic proteins. Exogenous steroid hormones might indirectly modify the joint lesions by alterations in capillary permeability, plasma proteins, and endocrine glands. Changes in the relative amounts of different plasma proteins diffusing into the joint space could modify the type and amount of protein combining with hyaluronic acid.

[There is a wealth of detail in this study which does not lend itself to abstracting and should be read in the original by the interested reader.] G. W. Csonka.

**Sensitization of the Skeleton to Vitamin-A Overdosage by Cortisol.** SELYE, H. (1958). *Arthrit. and Rheum.*, 1, 87.

It has been shown that excess or deficiency of a hormone can alter disposition to disease. In the experimental malady osteolathyrisms, in which there is excessive development of periosteal bone and proliferation of junction cartilages, ACTH or glucocorticoids have a preventive action, while somatotrophic hormone or luteotrophic hormone aggravates the condition.

With excessive doses of vitamin A there is osteoclastic bone absorption, and, in view of the findings in osteolathyrisms, it seemed possible that glucocorticoids would sensitize the skeleton to the action of excess vitamin A.

To test this possibility four groups of rats were used:

- (1) Untreated controls;
- (2) Given 20,000 I.U. vitamin A daily;
- (3) Given 1 mg. cortisol subcutaneously daily;
- (4) Given vitamin A plus cortisol.

The treatment was continued for 20 days, at the end of which there were no obvious changes in the long bones, the mandibles, or the scapulae, in the animals receiving cortisol or vitamin A alone. However, in the rats given cortisol plus vitamin A there was pronounced bone absorption, clearly indicating that cortisol greatly sensitizes the skeleton to the characteristic manifestations of hypervitaminosis-A. P. A. Nasmyth.



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